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FATIGUE IN AIRCRAFT PILOTS*

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ONE of the most significant problems in civil and military aviation relates to what is popularly known as "pilot fatigue." Conclusions about its nature or even its locus, however, are almost as numerous as the articles that have been written, since each depends largely on the interests or background of the author. Viteles[1] says that the word "fatigue" used both popularly and scientifically refers to three related phenomena: "An over manifestation in the form of reduced output on the task known as work decrement; a physiological state involving changes in organic functions and the production of chemical products of fatigue; and a feeling of fatigue or tiredness." Schneider[2] suggests that it "is a progressive flagging of efficiency, together with subjective sensations of loss of control." Grow[3] has advanced the hypothesis, based on wide experience in the field of aviation, that "fatigue is due to the excessive generation of nerve impulses and originates in the nervous tissue of the body."

The varieties of interpretation may be due in part to the fact that the word "fatigue" does not have a specific meaning in a scientific sense. It refers, generally speaking, to a related group of phenomena associated with loss of efficiency. In common usage, it is not unlike the word "unconscious" in psychopathology — a convenient category used to classify certain phenomena that are essentially unknown or not clearly understood, yet nonetheless real. The problem cannot be explained away, however, simply because agreement cannot be obtained relative to the phenomenon itself, its nature or its locus. In a practical sense, everyone, particularly a pilot after a long flight over difficult terrain and in adverse weather conditions, understands in a subjective sense what is meant by the words "nervous and physical exhaustion" and "fatigue."

In this discussion, an attempt to be practical is made, since the flight surgeon is always faced with practical problems. An operations' manager or flight officer, for example, may approach him with such questions as these: The pilots on certain routine operations are returning to their bases completely exhausted; is the flying time too long? Do they fly at too high altitudes without oxygen? Or is there something in the cockpit that affects them adversely, such as vibration, noise or poor illumination? Or, again, Captain Jones does not seem to be himself these days. He has "gone stale." He is tense, nervous and irritable, and shows poor judgment in making decisions while in flight. He used to be one of the ablest pilots in the flight group, but his flying is no longer trusted. Should he be grounded or sent away on a vacation? Finally, in the daily press are recorded accidents attributed to "pilot error." In the early stages of the war, the British pilots were evidently losing more planes in landing accidents on returning home from fighting abroad than during actual combat with the enemy. In civil aviation in this country, a large percentage of the accidents (often estimated at 80 to 90 per cent) are ascribed to pilot error. Do these pilots become so exhausted that their judgment is faulty when they make decisions or land? Do latent or minor visual defects in acuity, in night vision, in space perception and in sensory-motor performance become manifest or acute after long hours of fighting under intense emotional strain?

Since one cannot control and measure all the variables involved, the answers to such questions are indeed difficult. In a short discussion, one can hope to indicate only some of the more important contributing factors involved in pilot fatigue. Only brief mention is made, therefore, of the so-called "locus" of fatigue and of the accumulation of

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fatigue substances. Emphasis is placed on the variations in energy resources, such as oxygen and sugar, and, more especially, on several major contributing factors to fatigue, such as worry, personal maladjustments, lack of exercise, the effects of high altitude, poor selection of food, the excessive use of alcohol and tobacco, and certain factors in the cockpit of an airplane, such as noise and vibration. Finally, a study of fatigue in transoceanic airmen is discussed.

Locus of Fatigue

For many years, physiologists have attempted to locate fatigue in certain parts of the body — in the muscle itself, the nerve end plate, the nerve fiber, the synaptic junctions or the cortical cells of the brain. Numerous experiments have shown that the nerve fiber is almost indefatigable. These phenomena are demonstrated to students of physiology with the classic experiment involving a nerve-muscle preparation. A frog muscle, with its efferent nerves, is isolated; the nerve is stimulated until the muscle ceases to contract. Then, if the muscle is stimulated directly, it may react almost as vigorously as before. If the nerve is given a normal supply of oxygen and stimulated alone, it will continue to transmit impulses more or less indefinitely. By such procedures, attempts have been made to demonstrate the relative efficiency of the nerve and muscle and the possible location of fatigue in the nerve end plate or the synapses.[4] Although one can demonstrate that certain muscles are subject to loss of efficiency in ergographic studies, this sheds little light on the fatigue problem in aviation, in which the pilot's gross musculature is not used excessively. Studies of isolated nerve fibers have proved to be equally inconclusive concerning the basis of fatigue. Except for the role of oxidation in the efficient functioning of the nerve tissue, therefore, the implications of these experiments for pilot fatigue are not very direct.

It may be that the psychologists who have stressed the role of the higher cortical levels have more information to offer regarding pilot fatigue. They speak of mental "blocking," and they have demonstrated that, under certain conditions involving stress, there is a loss of efficiency in mental tasks.[5] This is especially true of the tasks that involve the more complex cortical functions, such as memory and delicate judgments of discrimination and choice.

In the field of vision, in which the processes involved are concerned essentially with minute muscle or nervous tissue, objective data on visual fatigue are very inadequate and inconclusive. Many authorities believe that the frequency with which ocular defects are observed in children (often estimated at 40 per cent) and in adults is directly related to the various strains imposed on the eyes in modern life. Unfortunately, however, little is known about the basic causes of these abnormalities or of the contributing factors to visual discomfort or loss of efficiency in visual work. Even in an applied problem in industry, such as the amount of illumination necessary to prevent visual discomfort, one finds a wide divergence of opinion among equally prominent authorities. The problem is complicated by the nature of the visual mechanism itself — that is, the retina is an extremely complex organ, being essentially an extension of the brain. It involves only a small amount of tissue, it adapts itself readily to changes in the environmental setting, and it apparently recuperates rapidly from ordinary stresses. In fact, many believe that the retina is indefatigable. Experiments dealing with the ocular muscles used in reading show that they are not easily subject to a work decrement. Carmichael and Dearborn[6] have failed, for example, to find evidence of fatigue of the muscles of the eye during six hours of continuous reading. The records were made by attaching electrodes to each side of the eye so as to record the action potentials of the ocular muscles during reading. Although the basis of visual fatigue is not clearly understood, it is essential to protect the pilot from variables known to accentuate visual discomfort, such as excessive glare from the clouds or sun, reflections from metal surfaces on the plane and poor illumination in the cockpit.

Accumulation of Toxic Substances

For many years, physiologists have attempted to associate fatigue with certain substances in the blood. At one time, many believed that lactic acid was the long-sought toxin.[7] Dill and his colleagues[8] have shown that the accumulation of lactic acid is related to fatigue but that, as an explanation of this phenomenon, such accumulation is more restricted than observers at first believed. Their experiments have revealed that the concentration of lactic acid in the blood remains a useful index to the degree of fatigue in one sort of activity, for example, that in which either the oxygen supply is deficient or the oxidative mechanism of the muscles is not competent to meet the demands placed on it. In studying a group of persons varying in athletic fitness or training, they[9] observed that in a famous Marathon runner there was no accumulation of lactic acid. In several untrained subjects, however, the accumulation of

lactic acid was very great. Those who were well trained were able to carry out the tasks with ease, whereas those in poor training who created large amounts of lactic acid were severely handicapped. The magnitude of the increase in lactic acid was closely related to the degree of fatigue, as indicated by other objective measures, such as the heart rate, respiratory rate and blood pressure, and by subjective evidence. That lactic acid is not the only factor was evidenced by the fact that many track records are broken by athletes in successive heats with large amounts of lactate in their blood. Furthermore, industrial workers doing heavy work, as well as miners at high altitudes, have been observed to have normal values for lactate in the blood. Other substances have been proposed as toxic factors in fatigue, such as ammonia and histamine, but further evidence is required to establish these theories.

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Exhaustion of Energy Reserves

A great deal has been written about the exhaustion of such energy reserves as sugar as a causative factor in fatigue. Experiments indicate that in very exhausting work — in a Marathon race or industry — the administration of glucose is of considerable value in maintaining efficiency. In work with a bicycle ergometer, Christensen et al.[10] observed that a very low blood sugar was associated with exhaustion and even sensory impairment. These effects were rapidly counterbalanced by the ingestion of glucose, and the subjects could continue the work for an hour or more. In heavy work, the preferred fuel is carbohydrate. If heavy labor is continued for a long time without food, the diminishing reserve of carbohydrate is associated with a falling respiratory quotient, a reduction in efficiency, a decreasing concentration of blood sugar and the appearance of acetone in the urine. Subjects in poor physical condition have low reserves of energy and a reduced capacity for transforming energy. Unfitted or untrained factory workers, therefore, may benefit from glucose or other readily available fuel taken between meals. They seldom work hard enough to exhaust their stores of sugar and other reserves. The effects are chiefly on the central nervous system. It is difficult to explain the reports of benefits from the ingestion of glucose in more sedentary occupations.[11] During very long and exhausting flights at high altitudes, pilots are benefited by taking such foods as glucose, which is easily assimilated between meals. From evidence obtained on heavy muscular work, however, it is difficult to understand how a pilot could consume his entire carbohydrate reserve, since the amount of gross musculature involved is so small. It appears, therefore, that the exhaustion of energy reserves in a pilot could hardly be an important causative factor in fatigue.

In the field of mental work, it is even more difficult to explain how the ingestion of sugar might counteract the effects of fatigue, although it is well known that the nervous system is primarily dependent on carbohydrate for fuel. The metabolic cost of mental work is very slight indeed. Laird's[12] report that fatigue in students doing simple psychomotor tests is modified favorably by the ingestion of certain sugars, such as maltose, has not been confirmed by other workers. In carefully controlled experiments on the metabolic cost of mental work, Benedict[13] found that sustained mental effort for several hours required only the number of calories in half a peanut. Other experiments have shown that in mental work it is not the involvement of the nervous system that increases oxygen consumption, but the musculature and other parts of the body associated with attention and sustained concentration. Hence, the fatigue from mental work is due in part to the increased muscular tonus associated with sustained attention.

In spite of negative findings in studies of mental fatigue, everyone is aware that subjectively it is a real phenomenon. Barcroft[14] suggests that mental fatigue, like chronic oxygen want, undermines normal self-control, with consequent exaggeration of feelings and mental abnormalities. He recalls that, after prolonged strenuous work during the war, he broke down and cried for no apparent reason, as he did at the termination of his six-day stay in the low-oxygen chamber. It is common for anyone, after prolonged mental effort or continuous overwork, to be aphasic, quick-tempered and lacking in self-control to a marked extent; quite trifling experiences make one furious. Barcroft intimates that the mentally overworked person who eventually seeks medical or psychiatric advice is possibly suffering from chronic oxygen want. Overexertion breaks down the tissues, owing to insufficient oxygenation, and a prolonged rest is required before adequate restoration can take place. Barcroft concludes that one cannot at present answer one way or the other the question whether mental fatigue is due to oxygen want. The impairment may be caused by a defect in any link in the oxidation process. But one can state with certainty, he avers, that "a given strain produces a greater degree of mental fatigue, as it would of muscle fatigue, when the oxygen supply is deficient than when it is ample." This observation is of significance for the pilot whose environment is known to be deficient in oxygen.

Psychologic Factors in Pilot Fatigue

Prolonged mental strain, anxiety, worry or fear appears to have a cumulative ill effect. Experimental studies of the increased oxygen consumption during emotional stimulation have given interesting results. Grollman[15] found that disturbances of anger or regret increased cardiac output, pulse, blood pressure and oxygen consumption. Totten,[16] in arousing emotions in the laboratory by electric shocks or loud noises, noted increases in oxygen consumption of from 0.5 to 25 per cent with the Benedict respiratory apparatus. The organism, however, can readily adjust itself to these temporary emotional situations. The cumulative ill effect of emotional and mental conflicts of a personal nature or of the strain involved while flying continually under adverse conditions gives rise to pilot fatigue, so-called "staleness" or a cumulative and permanent loss of alertness and efficiency.

In World War I, chronic fatigue or "flying stress," as it was often called, was not uncommon. Birley[17] describes a typical picture of a stale flyer in the Royal Air Force as one having lost keenness and become discouraged and uncertain of himself in the air:

> He loses flying judgment and has to force himself to go into the air. He is irritable, short of breath, and he attributes his condition to trivial causes. He sleeps less soundly and dreams of unpleasant flying experiences. Various kinds of mental conflict, such as indecision concerning the desire to fly and feeling unequal to the task, lead to complications involving loss of nerve and morale, at times suggesting the beginning of an anxiety neurosis. As his condition develops, he is eventually grounded, not only temporarily but permanently. The rate of the onset is gradual and is associated to some degree with the respiratory condition of the flyer. The first symptoms show an altered condition of the tone of the respiratory center of such kind that the regulation of breathing is no longer normal. There is also a loss of control in the voluntary system, lessened force of cheek and mouth muscles, and loss of tone in the stomach and bladder walls. Frequently, there is slight incoordination of the finer muscular movements and noticeable tremor of the finger and tongue.

All these symptoms suggest a similarity to the person in ordinary life suffering from overfatigue and bordering on what is commonly called a "nervous breakdown." These same ailments are often appearing in the present aerial war.

This problem has been discussed by Armstrong[18] under the terminology of "aeroneuroses." In his opinion, this illness is a chronic functional nervous disorder associated with flying. The pathogenesis consists of long-continued and profound emotional stress related to fear of accidents, economic and social insecurity and, possibly, nerve-tissue destruction producing general irritability, gastric disturbances, insomnia, sensory and motor hyperactivity and a deterioration of the higher nerve centers. This disorder is more frequently encountered in military than in civil aviation. In any large group of pilots, however, one is apt to find both borderline and acute cases. One of the chief functions of the flight surgeon is to know the airmen well enough so that they will discuss their emotional problems freely and openly. Pilots who are emotionally maladjusted, whether the cause be an unhappy marriage, finances or other troubles, are in danger in the air and should be grounded until their difficulties are straightened out.

If pilots are emotionally well adjusted, one might expect their acclimatization to high altitude to be more efficient because the sympathicoadrenal system, in Cannon's[19] terminology, is involved in emotional situations, as well as in acclimatizing to a lack of oxygen. If the sympathicoadrenal system is impaired or inefficient owing to chronic emotional stress, one might expect poor acclimatization to high altitude in somewhat the same way that emotion may interfere with the digestion of food. Cannon demonstrated that if cats became excited or struggled during an experiment, their ability to withstand oxygen deficiency was remarkably lessened. McFarland and Barach[20] observed that neurotic patients, as well as those suffering from "chronic nervous exhaustion," were more sensitive to oxygen deprivation than control subjects. This was manifested by greater frequency of fainting or collapse when they were placed in chambers deficient in oxygen, which thus simulated high altitude. It is commonly observed in the commercial air-transport planes that passengers who are very nervous are frequently the first to become air-sick or notice the effects of the altitude. A pilot may expect to find his ceiling becoming progressively lower if he is worried or emotionally upset.

Thus far, the difficulties involved in attempting to locate the phenomenon of pilot fatigue in any particular organ or toxin have been stressed. The nervous system and muscles do not seem to be subject to fatigue except under very limited conditions of oxygen lack, low blood sugar or excessive accumulation of lactic acid. Since the pilot's life is, for the most part, a sedentary one, with only partial use of the gross musculature, it is unlikely that the reserves of energy would be exhausted. The emphasis has been placed on psychologic factors, such as worry and mental and emotional conflict. In addition to the emotional

factors, lack of exercise, the effects of lack of oxygen at high altitude, the wrong kind of diet and the excessive use of alcohol and tobacco are major contributing factors.

Exercise and Pilot Fatigue

The trend of civilization from the earliest times has shown a close relation of the fitness of man and animals to their environment. If the environment changes, the animals must change to meet the new conditions. Airmen, to meet the requirements of prolonged sojourns at high altitude, must therefore attempt to adapt themselves so as to live comfortably and remain efficient under these conditions. In man's fight with the environment, the neuromuscular mechanisms have played a vital role. Under modern urban conditions, the muscles, lung surface and heart tissue are far in excess of what is needed for sedentary life. Unless the extra tissue is called into play, it atrophies and becomes a source of weakness. The highly trained athlete who suddenly stops training after leaving college is especially vulnerable to organ dysfunction. Large parts of the central nervous system are set aside for muscular activity, and this reserve must be used if it is not to become a source of danger.

The increase in emotional and mental disorders may also be related to the very great changes in modern, as compared to primitive, life. The glandular changes known to occur under emotional excitement, such as fear and anger, equip the organism for a struggle.[21] The secretion of adrenaline from the adrenal glands causes the blood pressure and heart rate to increase; the blood is directed from visceral activity to the muscles and brain; there is an increase in the rate and depth of breathing and a dilatation of the bronchioles of the lungs to facilitate the transport of oxygen to the arterial blood; the glycogen stored in the liver is released to provide extra fuel for the muscles; the pupils are dilated; and there is an increased rate in the coagulation of the blood in case of injury. All these changes have great significance in the survival of the organism in the event of a struggle. Under civilized conditions, however, there is less and less opportunity for an overt struggle, and there is less need for these physiologic changes. Continual emotional stress without overt activity may therefore have a cumulative ill effect on the efficiency of the organism in meeting situations involving stress. In piloting an airplane, there may be continual emotional stress, especially in adverse weather and over difficult terrain, without an excessive amount of physical exertion. At the end of the flight, the pilot should attempt to obtain some form of physical exercise, to keep in condition.

There is some evidence of concrete advantages from routine exercise for airmen. The pilots in the Royal Dutch Airlines apparently derived benefit from routine gymnastics during a week following long flights from the Continent to the Dutch East Indies and return. In a study of 50 Pan American Airways pilots in Miami, Dr. John T. Macdonald[22] observed an increase of four points in the Schneider index by moderate yet routine exercise over a period of several months. The benefits derived from such procedures were especially apparent in the older pilots. Further controlled studies are indicated to demonstrate the value of regular exercise for airmen.

It is a common experience to find that a man in poor physical condition is easily exhausted by mental and physical exertion: he is irritable and likely to have morbid thoughts, petty ailments and poor judgment; he may have a sallow complexion and dull eyes; and he frequently complains of constipation, headache, nervousness and insomnia. On the other hand, it is equally common to observe in a man of good physical condition evidences of mental and bodily vigor, such as alertness, cheerfulness, high morale, healthy complexion and capacity for arduous mental and physical work. It is believed that these two conditions are but the outward expression of physiologic differences within the body. There are no tests available to predict whether a pilot will make a serious error of judgment or lose emotional control in a crucial situation. For the most part, however, it is safe to say that errors of judgment or emotional confusion are the reflection of a poor or rundown physical condition. For this reason, a pilot must maintain a high degree of physical fitness.

Effects of Altitude in Accentuating Fatigue

It is well known that the important reactions in the human organism encountered at high altitude are due to the diminished partial pressure of oxygen.[23] There is no storage of oxygen in the human economy, as there is for other chemical substances like sugar and calcium, although the release of red cells by the spleen and bone marrow may be considered a reserve of oxygen in a limited sense. The blood is really the only storehouse, and its capacity is very limited. Hence, the body lives a hand-to-mouth existence and is dependent on a constant supply from the atmosphere. At 10,000 feet, a given breath of air supplies only two thirds as much oxygen as at sea level, and at 18,000 feet only half as much.

The average unacclimatized passenger is apt

to complain of certain physical discomforts while flying above 10,000 to 12,000 feet. In an extensive investigation carried out in experimental chambers at sea level and during prolonged flights at high altitude, the following reactions have been recorded voluntarily by the subjects and passengers.[24] The list is arranged in order of frequency and severity: slight frontal headache, which may become worse with increasing altitude; dizziness or vertigo on moving suddenly or in stooping over too rapidly; difficulties or irregularity in breathing and shortness of breath on exertion; digestive disturbances, especially gas in the stomach and in the intestines, and indigestion or slight nausea; slight sensory impairment on moving too suddenly, especially noticeable in alterations in vision; a tendency toward sleepiness or lethargy; and a sense of exhaustion and fatigue on exertion.

The response of the average passenger or pilot to high altitude may be influenced by a large number of variables. Since these factors are so essential in determining the altitudes where oxygen should be used and in answering other practical problems in civil aviation, a number of the more important ones are listed below. All these variables are either directly or indirectly related to the problem of pilot fatigue.

Height attained. There are great individual differences among the specific altitudes where the effects are first noticeable or become marked. Some persons may be affected at 8000 feet, and others at 16,000 to 18,000 feet. In a group of over 150 unselected subjects varying in age and physical fitness, in low-oxygen chambers at sea level during exposures of two to four hours' duration, the initial effects were significant in the average person at from 10,000 to 12,000 feet.[24] The effects may become quite marked at 14,000 to 16,000 feet and dangerous at 18,000 to 20,000 feet. The upper limit of consciousness in unacclimatized man appears to be about 25,000 feet.

Rate of ascent. In a series of experiments on rate of ascent, it was observed that if the high altitude is attained gradually,—that is, in an hour,—the effects are considerably less serious than during an ascent to similar altitudes within fifteen minutes. In a number of subjects who showed very poor responses following rapid ascents to 16,000 feet, a satisfactory acclimatization was made during repeated experiments in which the ascent was extended over one hour and fifteen minutes. During a slow ascent, the mechanisms of adjustment to the reduction in oxygen pressure have an opportunity to function. On the trans-Pacific flights, where from one to three hours may elapse before the ship is leveled off at the desired altitude, slow ascents are physiologically favorable to the passengers and flight personnel.[25]

Length of exposure. Moderate altitudes of 6000 to 10,000 feet may be tolerated over long periods (eight to fourteen hours) without apparent ill effects. This does not seem to be so at 12,000 to 14,000 feet. Although the mechanisms of acclimatization may be effective at moderate altitudes, the opposite appears to be true at higher altitudes. Deterioration may set in, and the physical symptoms during the flight may be quite unpleasant. Older pilots find it advantageous to use oxygen at and above 9000 feet for flights of more than two or three hours' duration.

Amount of physical exertion. The effects of high altitude tend to be accentuated during exercise. This is of particular significance in stewards, whose chief activity involves the preparation and serving of meals and making up the berths while in flight. On this account, the other members of the flight crew should not make excessive demands on the steward during flights at high altitudes. Care should be taken not to make too sudden movements or to stoop over too quickly because of cerebral anemia or lack of blood and oxygen in the brain and the increased susceptibility to fainting. Passengers should be urged to remain quietly seated following a meal at high altitude, so that the blood will not be diverted from the digestion of food to the muscles. Also, the airmen might find it advantageous to arrange their meals aloft so as to relax for a short time following a meal before going on duty again.

Roughness of air and sudden movements of plane. Air-sickness becomes greatly accentuated at high altitude. Because of the combined effects of oxygen lack and rough air in interfering with the digestion of food, special precautions should be taken in the kinds of food ingested while one is flying under adverse conditions at high altitude.

Importance of Pilot's Diet

Among the factors that may affect the efficiency of a pilot, no one is more significant than his food. This is especially true during flying, because of the effects of oxygen lack on digestion. Several controlled experiments have been carried out on the effects of reduced oxygen pressure on the digestive processes. In studies with dogs, Delrue[26] observed a marked diminution of gastric secretion, lasting from two to three days, in animals taken from a low to a high altitude. Van Liere, Crisler and Robinson[27] found that the emptying time of the stomach was prolonged in proportion, so that at 20,000 feet the dogs had food

in their stomachs twenty-four hours after ingesting it. In additional experiments on dogs, these workers[28] found that oxygen deprivation altered the hunger contractions of the animals, so that, under acute conditions and also following the experiment, the contractions were considerably diminished.

These findings on animals were then checked on 8 medical students in a low-pressure chamber.[29] A barium meal was given, so that fluoroscopic views of the stomach movements could be followed. The degree of retardation of the emptying time of the stomach varied roughly in proportion to the degree of oxygen deprivation. The altitudes where the first changes were noted for the average person at rest were between 6000 and 8000 feet. These and other experiments indicate that, although the effects of the reduced oxygen pressure at moderate altitudes are not severe, there is ample evidence that both the airmen and the passengers should take precautions in the amount and kinds of food ingested aloft.

At high altitudes, the pilot or passenger may become uncomfortable or distressed by abdominal bloating due to the expansion of gases in the intestine during the ascent. It is well known that the gases accumulated in the digestive organs expand as the external pressure falls, so that at 18,000 feet, — that is, half an atmosphere of pressure, — the gases in the digestive organs expand to double their volume. This may lead to an unpleasant pressure on the abdominal wall and diaphragm, thus decreasing the normally available space of the thoracic cavity. When gas forms continually in the stomach and intestinal tract, it may be the result of either excessive worry, fear or other emotional disturbances that interfere with the digestive processes, as explained above, or a diet too rich in foods that are easily fermented, such as green vegetables and certain carbohydrates.

In general, it may be said that the most desirable diet for the airman or passenger previous to a flight or while in the air is one of high caloric value, which is easily assimilated. Carbohydrates, such as glucose and cane sugar, and the products derived therefrom are highly recommended. On the eve or day of a flight, only a limited amount of leguminous or green vegetables and fruits should be eaten. Highly spiced or greasy foods should very definitely be avoided, especially cellulose, the skeleton of most plant structures and of plant cells. Cellulose is also found in other portions of starch grains and leguminous vegetables, such as beans. By diminishing the formation of intestinal gases by the control of the kinds of foods ingested before or during a flight, the pilot is certain to be more comfortable and more efficient while performing his duties.

Interesting results have been obtained in the Pan American Airways System in special cases of fatigue and chronic minor illnesses in which pilots have supplemented their diets with vitamins and minerals. This has been particularly true in certain pilots flying in Alaska or Central and South America, where fresh vegetables and other essential foodstuffs have been lacking in their diets. A study of night vision in pilots with the Hecht adaptometer was made on 200 pilots.[24] Two marked cases of vitamin A deficiency and 7 cases of borderline or questionable abnormality were observed. Controlled studies are being made at present on large numbers of military and civilian pilots. A more exact indication of the extent of dietary deficiencies should be available in the near future. Better objective tests, which might reveal deficiencies of each vitamin or mineral, are needed.

Another major consideration in the diet of airmen and passengers is the quantity of food to be taken previous to and during flight. Under most conditions of modern life when muscular activity is limited, the average person probably eats far too much. The sleepiness and lethargy following an excessively large meal are well known to everyone. In view of what has been stated above about the formation of intestinal gases at high altitude, as well as the general slowing up of digestive processes and the slower movement of food through the intestinal tract, the amount of food ingested before and during a flight should be greatly curtailed. There is no question that mental and physical efficiency, as well as general comfort during a flight, can be greatly influenced if smaller amounts of the right kinds of food are eaten.

Effects of Alcohol

A large number of experiments on the psychologic effects of alcohol show that it decreases efficiency because of its apparently depressant influence on the nervous system. The initial stimulation is probably due to overcompensation on the part of the organism to ward off the depressing effects. Even small doses of alcohol have been shown to decrease reflex irritability, slow up muscular movements and reaction time, raise sensory thresholds, impair attention and concentration, and, after a time, reduce the natural spontaneity of mental functions.[30] Experiments on both mental and physical fatigue reveal that alcohol hastens loss of function and impairs efficiency. The improvement so often noted is due to abolishment

of the sensations of fatigue. In athletics, such as in crew or track, the transport of oxygen from the blood to the muscles is impaired, and it is for this reason that even small amounts of alcohol are detrimental and cut down performance by the fraction of a second necessary to win a race.

Recent research on the effects of alcohol has revealed a number of interesting facts for pilots and air passengers. Possibly one of the most direct effects of alcohol on the organism is that of diminishing the utilization of oxygen in the tissues. There is a close similarity between the behavior of a person suffering from acute oxygen deprivation on a mountain, in an airplane or in a low oxygen chamber at sea level and that of a subject under the influence of alcohol. The effect on the nervous system under both conditions is essentially the same — that is, a deficiency of oxygen is delivered to the tissue. At high altitude, there is a deficiency of oxygen in the inspired air, and under alcoholism there is a hindrance in the transport of oxygen from the blood to the tissues.

The frequent references to the similarities in behavior between the effects of alcohol and of oxygen want (anoxia) and the fact that acute alcoholism could be counteracted by breathing excess carbon dioxide led McFarland and Barach[31] to analyze the concentration of alcohol and lactic acid in the blood following the ingestion of standard amounts of alcohol in an oxygen chamber filled with air and at other times with excess oxygen (50 per cent) and excess carbon dioxide (2 to 5 per cent). The experiments showed that on the average both the blood alcohol and lactic acid were diminished during the breathing of excess oxygen and carbon dioxide as compared to the breathing of air. On the other hand, the alcohol was oxidized more slowly and the subjective effects accentuated when air deficient in oxygen was breathed. The experiments were repeated at 17,500 feet and 12,200 feet in the Andes, with similar results.[32] The significance of these findings for airmen is obvious. The effects of alcohol are greatly accentuated at high altitudes, and efficiency following the ingestion of alcohol is therefore impaired proportionally. The passenger who boards an airplane after drinking heavily may fall asleep quickly and forget his fears and worries. If the air is rough, however, he usually awakes and is more subject to airsickness. The pilot at that time, on the contrary, must be alert and efficient, and nothing should be involved to impair his nervous functions during the flight.

Effects of Tobacco

There are very few carefully controlled studies of the effects of smoking, and even less information dealing with the effects of tobacco at high altitude. Modern advertising has tended to distort the facts regarding the effects of tobacco. The evidence from reputable university laboratories does not uphold the contentions frequently made that one brand of cigarette causes less acidity than another, or that any "lift" is due to an increase in blood sugar. It is obviously absurd that smoking necessarily goes with being a good athlete, explorer or aviator, as many cigarette advertisements imply.

The stimulating effect of tobacco is due to the nicotine, which is an alkaloid. Nicotine is poisonous, and in small quantities has an effect similar to other alkaloids (morphine, strychnine and cocaine). The commonly alleged soothing effects of smoking tobacco are due primarily to the nicotine. A number of carefully controlled studies indicate that smoking gives rise to the following reactions in the organism, largely through stimulation of the autonomic nervous ganglia: an increase in pulse rate, especially noticeable when one smokes before breakfast; an initial rise in systolic blood pressure, followed by a fall immediately after the smoking period, which may account for the dizziness often noticed by the inexperienced smokers; constriction of the blood vessels, particularly in the periphery of the body; a slight impairment in keenness of vision — since the eye is the most sensitive of the special senses, these effects are manifested in visual functions more readily than in hearing; inhibition of digestive movements of the stomach — it is from this effect that the smoker may temporarily allay his hunger; effects on the surfaces of the lungs, which give rise to breathlessness on exertion. There is some evidence that the carbon monoxide from smoking affects pilots adversely; although the amounts are small they are believed by many to be damaging at high altitudes and relatively innocuous at sea level.

During World War I, a series of studies was carried out on aviators relative to the effects of smoking.[33] The results indicated that in 75 per cent a single cigar or the inhalation of one or two cigarettes had definite though temporary effects on vision and caused an increase in pulse rate and a rise in blood pressure. The visual effects were manifested in terms of reduced visual acuity and ocular muscle balance. Only a few nonsmokers were studied. In these cases, some giddiness occurred at eighteen to twenty minutes from the start, and was accompanied by slight nausea.

It is therefore obvious that excessive smoking has a detrimental effect on the pilot's acclimatization to high altitude. It tends progressively to

lower his ceiling, just as it would impair his performance in a track or crew race at sea level, owing to the unknown effects on the lungs and circulation. It also impairs his digestive processes and the assimilation of food. The airman is warned against smoking before breakfast and against the excessive inhalation of cigarette smoke at all times.

Effects of Noise and Vibration and Other Variables in the Cockpit

Certain variables in the cockpit of an airplane are contributing factors to pilot fatigue. These effects are less extreme in modern civil aircraft than in military planes. It should be kept in mind, however, that the noise and vibration in the cockpit are much greater than those in the passenger compartments of most civil aircraft.[34] Unfortunately, there are few controlled studies dealing with the effects of noise and vibration in aircraft on pilot performance and fatigue. Many pilots believe that these are significant factors, especially in flights of extended duration. A number of fatiguing influences that should be carefully controlled are as follows: the pilots' seats should be free of vibration and located conveniently near the controls and instruments; the navigating tables should be cushioned, to prevent excessive vibration; the cockpit should be well illuminated at night; radium paints should be eliminated on the dials because of the possibility of noxious effects from the radium; metal surfaces, which give rise to glare, should be eliminated; attempts should be made to reduce the static in the earphones; and the ventilation and temperature should be well controlled, to avoid extremes. All these variables may contribute to pilot fatigue individually or collectively. The flight surgeon should study every factor that affects the health or efficiency of the pilot. Most of these adverse conditions can be corrected by aeronautical engineers.

Experimental Studies in Trans-Pacific Flights

A study of fatigue in transoceanic airmen was carried out on a routine flight of the Pan American clipper between Alameda, California, and Manila, Philippine Islands, and return, to analyze the fatiguing effects of prolonged flights at altitudes averaging 9460 feet on 17 airmen and 11 passengers. The total flying distance of 14,141 nautical miles involved one hundred and twenty-two and one-half hours in the air. A series of physiologic, biochemical and psychologic studies were made at the various island stations. The following conclusions may be drawn from the data obtained on these airmen and passengers:

The subjects, both airmen and passengers, maintained a high degree of neurocirculatory efficiency throughout the flight, as judged by the individual items and composite score of the Schneider index. When the test was given in the basal state, — that is, before ascent, — none of the airmen tested below +7, a score frequently related to a significant degree of fatigue or unfitness in aviators. Of one hundred and forty-two tests in the basal state, only 2 subjects tested below +10, the average being +13, which is close to the mean of +14.8 for college athletes. The average basal state (fifty-four tests) was +11.5, only three tests falling below +7 throughout the flight. The mean score for the group at high altitude was +10.8. In a total of ninety-six tests given at a mean altitude of 9500 feet, only four fell below +7.

There appeared to be a general tendency toward low blood pressure as the flight progressed that was similar to the blood pressure observed in acclimatized workmen at high altitudes in the Andes. Six of the 8 airmen (the mean age for the group was thirty-two years) had systolic blood pressures below 110. The initial response to altitude usually showed an increase in pulse rate and an increase in systolic blood pressure, followed by a well-controlled fall to normal values if the subject remained at rest.

As the flight progressed, the pulse-rate tended to show a greater increase after exercise and to take longer to return to normal. As might be anticipated, this was also true at high altitudes.

There was a consistent decrease in the Schneider indexes in Manila. This was related to the increased pulse rate caused by the high humidity and temperature of that region. After the subjects rested two days in Manila and slept in air-conditioned quarters, there was an improvement in the Schneider indexes. After a rest period of one week in Honolulu, there was a slight decrease in the mean Schneider index for the 8 airmen.

There was a tendency toward polyuria in these airmen, as commonly observed in athletes previous to competition, particularly in those who shared the greatest responsibility in handling the ship. As the flight progressed and the airmen became acclimatized, the polyuria diminished.

The partial pressure of oxygen and carbon dioxide in the alveolar air and arterial blood of these airmen was similar to values considered normal for acclimatized men at similar altitudes,

and suggested that the added burden of flying the ship had no impairing effect on the respiratory mechanism. The mean alveolar partial pressure of oxygen in the acclimatized airmen averaged 4.8 mm. higher than in unacclimatized passengers during rapid ascents to similar altitudes.

There was an increase of approximately 10 per cent in the red-cell counts at high altitudes. After five or six days at sea level, the counts returned to more normal values in 9 of the 11 airmen. Even after eleven days at sea level, however, 2 subjects had counts 16 per cent and 18 per cent above the usually accepted value of 5,000,000 for men at sea level; this suggested a more stable acclimatization in these men.

The normal nonprotein nitrogen, blood sugar and cholesterol values suggest that there was no serious upset of the protein, carbohydrate or fat metabolism of these airmen. The normal values for blood sugar indicate that there was no intense emotional excitement and increased secretion of adrenaline during flight.

There were only slight alterations in the visual and mental tests — primarily, quickness of reaction time for meaningful material, close attention and memory — at 10,000 to 12,000 feet, as compared with sea-level norms.

In general, the conclusion may be drawn from this investigation that the 17 airmen studied during typical trans-Pacific operations became acclimatized to the high altitude and maintained a high degree of mental and physical efficiency throughout the flight. The 11 passengers of average age and fitness studied, although not manifesting the same degree of acclimatization as the airmen, showed no objective signs of fatigue or physical distress.

Summary

In this discussion of fatigue in aviation, an attempt is made to analyze some of the more important contributing factors to pilot fatigue. It is shown how the attempts to locate fatigue in certain tissues or organs have not proved to be very revealing in solving practical problems related to subjective fatigue and exhaustion. Likewise, the search for a fatigue toxin, such as lactic acid, has brought to light many significant variables related to fatigue, but the relations have been more restricted than was at first expected. Furthermore, it is shown that a pilot whose muscular activity in flight is limited could hardly exhaust the energy reserves sufficiently to explain the fatigue and exhaustion often observed in airmen. The essential variables in the phenomena of acute or chronic pilot fatigue and exhaustion are ascribed to psychologic factors such as emotional stress, regardless of whether it is related to adverse flying conditions, fear of accidents, economic and social insecurity, and unhappy marital adjustments. The major portion of the discussion is related to an analysis of certain contributing factors in pilot fatigue, especially lack of exercise, the reduced tension of oxygen encountered while in flight at high altitudes, the poor selection of food and the excessive use of alcohol and tobacco. Also, certain physical variables in the cockpits of airplanes are discussed as other contributing factors to fatigue, such as noise, vibration, poor illumination, glare, static from the radio and poor regulation of the ventilation and the temperature. Finally, the results obtained in a study of transoceanic airmen are analyzed to show the effects of long flights at moderately high altitudes.

113 Morgan Hall
Soldiers Field

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THE TREATMENT OF WAR WOUNDS OF THE BRAIN*

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IT is quite obvious that a discussion of the treatment of war wounds is most pertinent at the present time. This paper is designed to cover not only actual gunshot wounds of the brain but also similar injuries due to fragments from shells and from bursting bombs, the latter being probably even more frequent in this war than the ordinary types of wounds from penetrating missiles.

PROPHYLAXIS

Since this subject is so obviously a war topic, a few remarks concerning what may be done by way of prophylaxis to lessen the severity of head injuries appear to be in order. In the first place, it would be most desirable if all soldiers could go into action with closely cropped hair. This would not only minimize the amount of hair that would be driven into the brain in penetrating injuries but would also prevent a great deal of infection of the lacerated scalp wound from the long hair, which becomes matted with blood and frequently incorporates itself within and contaminates the laceration. Furthermore, the shaving and sterilization of the area around any such wounds would be infinitely easier.

Secondly, tetanus toxoid has been shown to be a most valuable prophylactic agent and should be given to all soldiers and civilians likely to be involved in enemy actions. The usual dosage consists in 1 cc. subcutaneously as a first injection and a second injection of the same amount two or three months later; a third injection after another two or three months is advisable. If it is known that this series of immunizing injections has been complete, 1.0 cc. of tetanus toxoid should be injected subcutaneously at the time of injury; in the absence of complete immunization, 1500 units of tetanus antitoxin should be given immediately in all cases with compound injuries.

Thirdly, the sulfonamides should be given by mouth at the earliest possible opportunity after a compound injury of any kind has been received. An initial dose of 6 gm. of sulfanilamide should be given by mouth if it is possible for the patient to swallow; if the patient cannot swallow, it should be given through a nasal tube. Subsequent doses at four-hour intervals, so that patients receive approximately 6 gm. daily, should likewise be administered.

GENERAL PRINCIPLES

It must be remembered that all penetrating brain wounds due to shell fragments, bullets, bomb fragments and so forth are compound fractures. One of the greatest essentials is to get these patients to a hospital or post where complete treatment can be carried out for their wounds at the earliest possible moment. So far as immediate or delayed surgical shock will permit, it is highly desirable that operative treatment, when it is indicated, be undertaken within twelve hours of the time of the infliction of the wound, and earlier if possible, since the sooner these wounds can be débrided the less the chance of subsequent infection and thus of complications, which so often either are fatal or produce untoward late effects.‡

It must also be remembered that many patients, especially those who have multiple wounds elsewhere on the body or extremities, may first of all need treatment for serious shock. This must be combated in all possible ways by warmth, hot drinks, infusions of serum or plasma or transfusions of blood, the guarded use of small doses of morphine, and quiet and complete rest so far as this is obtainable. Infusions and transfusions can be carried out while the patient is being operated on; they should not be delayed too long before operation is undertaken. In addition to the care de-

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‡It is possible that with the present more perfect methods of wound débridement, together with the use of sulfonamides, operation with primary closure may be delayed from twelve to twenty-four hours if necessary.

voted to the wound of the brain, multiple wounds in other parts of the body, such as those of the chest and extremities, should be looked for and treated.

Preoperative Preparation

As soon as possible, stereoscopic x-ray films of the head should be taken in the lateral position, as well as in the anteroposterior and posteroanterior positions. The whole head should then be shaved carefully, and a careful examination for multiple skull wounds should be made. A brief neurologic examination is also indicated, since this may be of great value in checking the subsequent status of the patient if complications such as postoperative hemorrhage arise. A small dose of morphine, not over ⅛ to ⅙ gr., may be given about half an hour before operation is contemplated, but not until all neurologic data are noted and not, of course, if the patient is unconscious or extremely drowsy.

Anesthesia

In almost all cases, local anesthesia is the method of choice for gunshot wounds of the skull and brain. This consists of a 1 per cent solution of novocain to which has been added 4 drops of adrenalin (1:1000) per ounce. If the initial preoperative dose of morphine has not been sufficient to quiet the patient, a second dose may be given during the course of the operation. There are obviously times when local anesthesia cannot be used, namely, when patients are extremely restless and unco-operative, and especially when multiple wounds elsewhere in the body require operation at the same time. In such cases, ether anesthesia or a combination of Avertin and ether is probably the anesthetic of choice. When highly trained anesthetists are available, intratracheal ether or, for short operations, possibly intravenous Pentothal may be extremely useful and may perhaps to a limited extent supersede local anesthesia, although novocain for this type of injury is highly satisfactory in the vast majority of patients.

Operative Treatment

The general idea of operative treatment for all compound injuries is a thorough and careful débridement of the contaminated tissues, together with the removal whenever possible of such foreign bodies and bone fragments as have been retained, without added damage to the surrounding areas. This applies to brain wounds just as it does to those of the extremities, although obvious difficulties arise so far as the brain is concerned because of the undesirability of sacrificing any more normal brain than is absolutely necessary, and because in certain cases more damage might be done in searching for a foreign body, especially for small fragments, than by leaving these fragments alone. Furthermore, the danger of hemorrhage from the deeper portions of the brain must always be carefully considered and prepared for. Again, as a general rule, if patients with gunshot wounds of the brain have been operated on early, — up to twelve hours of the time of the infliction of the wound, — if the operator is satisfied that a complete débridement has been done, and if the patient can be kept under observation by the operator for at least ten days or two weeks, the wound should be closed tightly, without drainage. It is possible that with the use of sulfonamides by mouth or intravenously, together with the local instillation of sulfanilamide or sulfathiazole powder into the wound itself, many more of them can be completely closed than was possible before the introduction of chemotherapy. This, however, is not yet entirely clear, and it is probably well, even with chemotherapy, not to close wounds that have been operated on after the twelve-hour period.

After operation, 1500 units of tetanus antitoxin should be given intramuscularly if a prophylactic dose was given immediately after the infliction of the wound. It is also advisable to give gas-gangrene antiserum to all these patients.

Wounds without Dural Penetration

After the usual preparation and sterilization of the scalp around the area of injury, the wound should be excised, but only far enough beyond the lacerated, contaminated edges to take in contaminated tissue. Contused but uncontaminated tissue should not be excised. The instruments used for this excision should then be discarded, along with the tissue excised. When there is a linear fracture without positive evidence of depression and when the operator is sure that there has been no intracranial damage, the wound may be treated as a scalp wound, with primary closure if the wound has been operated on early. If the cranium is depressed, one should make one or more small burr openings around the area of depression and then elevate the uncontaminated skull with some proper, smooth instrument. Again, the instruments used for this bone removal should be discarded. Occasionally, an experienced neurosurgeon may consider it practicable to replace bone fragments when early operation and thorough débridement have been performed; but such

replacement should never be attempted by inexperienced operators. Irrigation of these wounds with physiologic saline solution during débridement is recommended by many neurosurgeons but is deemed inadvisable by others. Sulfanilamide or sulfathiazole powder should be dusted into the wound at the conclusion of the operation.

If the patient shows marked signs of localized contusion of the brain under the area of fracture, an area of bone should be taken out, whether it is depressed or not, and the dura inspected. If the latter is tense and discolored a deep bluish black, signifying an underlying clot, and if the operator is satisfied that his débridement has been perfect, the dura should be incised, the clot evacuated, and the dura then resutured completely and carefully with fine silk.

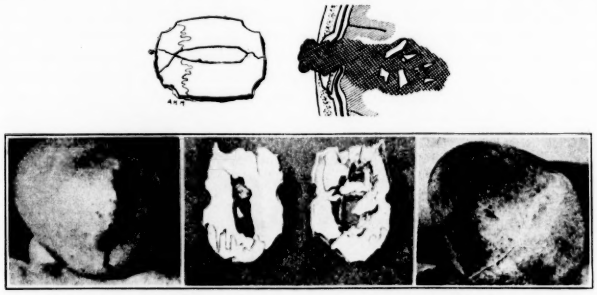

FIGURE 1. *Gutter Type of Wound. (Modified from Cushing.[1])*

The drawings are diagrammatic representations of this type of wound, showing the bone fragments "showered" into the brain. The photographs show a typical wound, before and after operation with primary closure, together with the solid area of bone and the bone fragments removed.

Wounds with Dural Penetration

Under this heading are included all the more serious types of brain wounds due to missiles of war. In a general way, they may be divided roughly into five types: the gutter type of wound, in which the missile has plowed a furrow through the scalp and often through the bone as well, and in which a shower of bone fragments, together with other debris, such as hair and cloth-

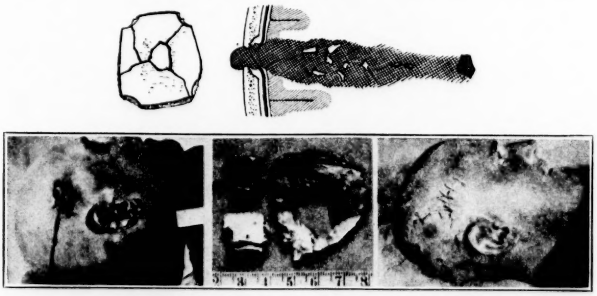

FIGURE 2. *Penetrating Type of Wound. (Modified from Cushing.[1])*

The drawings are diagrammatic representations of this type of wound, with a metallic shell fragment lodged at bottom of track. The photographs show a typical wound from a single large fragment, before and after operation with primary closure, together with the excised area of bone and the bone fragments. Note the "tripod" incisions, which are useful in wounds of this kind.

ing, has penetrated the underlying brain to varying distances, sometimes going in as far as one of the cerebral ventricles (Fig. 1); simple penetrating wounds, which are usually due to a rather large, single metal fragment that has carried in with it fragments of bone and other debris and has lodged somewhere within the brain, not infrequently penetrating the ventricle and sometimes crossing to the opposite side of the brain from that on which it entered (Fig. 2); penetrating wounds from multiple and often small fragments, particularly bomb splinters — this type of injury has been particularly prevalent in World War II; through-and-through or perforating injuries, which usually have a small wound of entrance and a much larger wound of exit, with a certain number of bone fragments carried in along the track; wounds involving one or another of the air sinuses, more particularly the frontal and ethmoid sinuses, in which subsequent complications, such as cerebrospinal-fluid leak or intracranial aerocele, may develop.

The gutter type of wound and wounds due to a large, single penetrating fragment. The operative treatment of wounds of the first two types may be considered together, since they are essentially similar in most of their aspects and in general require the same type of treatment.

After careful excision of the contaminated portion of the scalp, radiating incisions should be made from the area of scalp laceration, usually in the form of a tripod, so that the flaps thus created may be retracted and an adequate exposure of the fractured area secured. The break in the skull is a relatively small round opening or a rather large, irregular hole in wounds due to a large metal fragment, and the bony defect is a long elliptical area in gutter wounds. Four burr openings are made surrounding this bony defect and including the depressed fracture area,

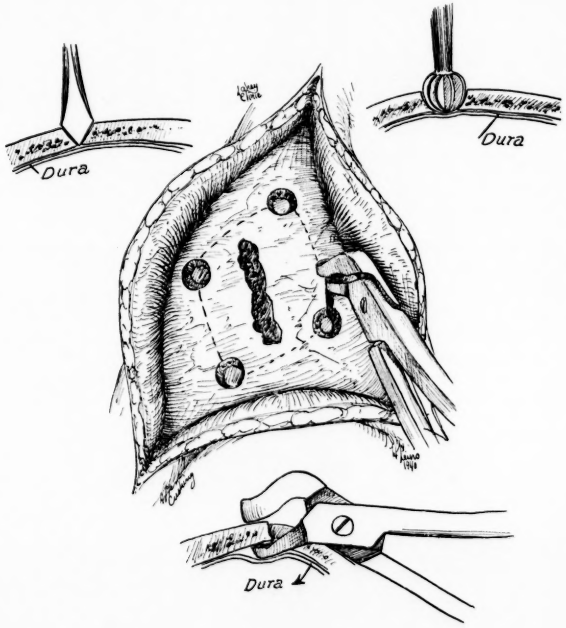

FIGURE 3. *Excision of the Bony-Penetration and Depressed-Skull Area by Bone-Cutting Forceps after Exposure of the Area by Reflection of the Scalp. (Modified from Cushing.[2])*

and these openings are connected with bone-cutting forceps, a procedure that enables one to lift out the whole bony area intact and thus to expose the dura with either a small or a large perforation (Fig. 3). At this point, the procedure of choice varies according to whether or not an electrosurgical apparatus, together with adequate suction, is available.

If these two adjuncts are not at hand, a method similar to that employed during the last war, as advocated by Dr. Harvey Cushing, is in order. If the patient is under a local anesthetic, he is asked to strain or cough, and by this means considerable amounts of clots of semisolid contused brain may be expressed through the hole being withdrawn from time to time and such material as has been sucked up into it is then discharged out of the field of operation (Fig. 4). In this way, all bone fragments and other debris may eventually be completely removed from the contaminated area in the brain. It is essential to remove every indriven bone fragment in this manner, and it is likewise advisable to remove the metal foreign body, which as a rule is found down at the bottom of the track, if this can be done without undue difficulty and without further damage to the brain. The metallic fragment can sometimes be located with the catheter, and a delicate, alligator forceps can then be inserted

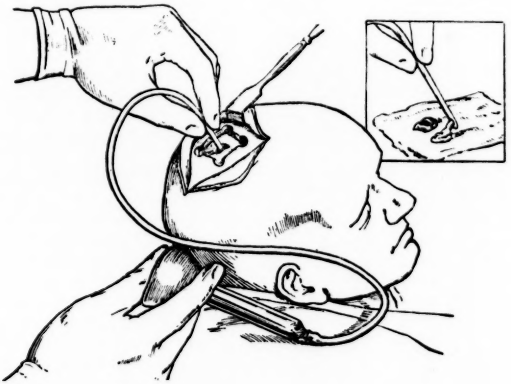

FIGURE 4. *Catheter-and-Syringe Method of Débridement of the Track in the Brain. (Cushing.[2])*

The softened, disorganized tissue is sucked out; the bone fragments and other foreign bodies are palpated with the catheter and removed by delicate forceps.

in the dura, and such material may then be wiped gently away from the remainder of the wound. Indeed, small bone fragments may sometimes be thus extruded. A soft-rubber catheter of suitable size is then inserted gently through the hole in the dura, and with this catheter as a means of palpation, bony fragments along the track of the missile are gently searched for and removed either by gentle suction with a syringe attached to the end of the catheter or by a grasping of the fragments with a delicate forceps and their extraction in this way. Gradually, as the catheter is inserted farther and farther in the track, the area is cleaned out by careful, not too vigorous suction on the catheter; thus, devitalized brain tissue, clots and other debris are drawn up into the catheter itself, the catheter and the foreign body picked up and thus extracted. When the metallic fragment is of magnetizable material, it is often useful to insert a long, round-ended nail down into the track in the brain so that it touches or nearly touches the metallic fragment. When this has been done, a powerful electromagnet is brought up to the end of the nail, and often the withdrawal of the magnet and the nail also withdraws the foreign body (Fig. 5). It is a long tedious process to clean out thoroughly a deep penetrating wound by the means thus described, and when this method is used, it is of the utmost importance not to disturb the dural edge and not to get out into normal brain outside the track created by the foreign body and bone fragments. At the end of such an operation, it is probably advisable to dust sulfanilamide or

sulfathiazole powder into the cleaned-out brain area; if the débridement is thought to be complete, if the operation has taken place within twelve hours of the injury, and if the patient can be followed for ten days or two weeks by the operator, primary closure should be made.

If an electrosurgical apparatus, together with strong suction, is at hand, a somewhat different procedure is preferable to the time-consuming and sometimes inadequate débridement possible by the catheter-suction method. Although it has

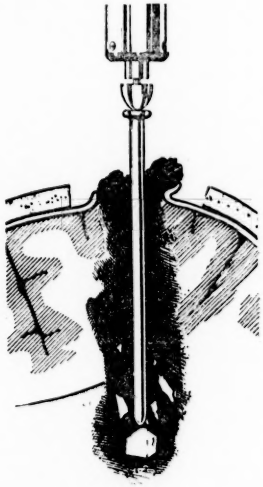

FIGURE 5. *Blunt-Nail and Electromagnet Method for Extraction of Magnetizable Metal Bodies. (Horrax[3]; reproduced by permission of the publisher.)*

not as yet been tried in combat or other war areas, I believe that the following procedure would be particularly applicable in wounds outside the motor and speech areas.*

After exposure of the dura by the means already described, the membrane should be incised to a distance of perhaps a centimeter in a circular fashion outside the area of dural penetration, and then the whole track in the brain should be excised, together with its contained elements, in exactly the same way as a similar wound anywhere else would be excised. With the electrosurgical apparatus, an area slightly outside the actual track of the missile or bone fragments should be sealed off, that is, the blood vessels on the surface should be sealed off around this area, and the brain incised in this coagulated area outside the track. Then, by a combination of strong suction, using a metal sucker, and with the electrosurgical coagulating current constantly applied to this sucker, one can clean out the soft brain surrounding the track, together with the clots and other debris (Fig. 6). If larger bone fragments are encountered, they can doubtless be taken out by the strong suction itself, or if they are too large for this, they can be extracted with delicate forceps. In this way, a core of tissue including a small amount of uncontaminated brain outside the track is completely removed by the combination of suction and electrocoagulation, the latter being employed to sterilize the area at the outside of the track as one proceeds. As the core of tissue is gradually removed, one can insert a flat spatula along either side of the cavity created, and thus débride the whole area under direct vision (Fig. 7). I am convinced that a much more complete and thorough débridement of all possible elements contained in the track can be accomplished in this way than by the older method. Any possible bleeding set up as this procedure progresses can be rapidly stopped by the electrocoagulation; finally, if a large foreign body requires removal from the bottom of the track, it can be seen and picked out very readily. When ventricular penetration occurs, the ventricle can be inspected and any debris removed from it. Again, as in the older method of treatment, wounds that have been completely débrided by the method just described should be closed primarily when patients are operated on within twelve hours after injury, after the local application of sulfanilamide or sulfathiazole powder within the wound.

When patients are operated on after the twelve-hour period following an injury, sometimes after one, two or even three days, the wounds show varying degrees of infection, which has sometimes gone on to an extremely foul-smelling herniation or fungous formation of the brain, with bone fragments and other debris extruding through the brain track. These wounds must be opened widely, and additional bone must usually be taken off around the area of penetration so that the dura can be incised in radiating fashion, thus relieving the almost certain constriction that exists at this point and is bottling up the infection inside. All devitalized tissue, bone fragments and other debris should be completely sucked away down into the track, which should be treated by open drainage of one form or another just like a brain abscess. It is my opinion that probably the best form of drainage in a case of this kind

*I am informed by a neurosurgeon recently returned from England that this proposed method has been used there with excellent results.

is to insert gutta-percha tissue down to the bottom of the track, which is then packed widely open over this tissue with gauze. In any event, the track should be held widely open by some means, and in these cases it is probably best not to dress the wound for two or three days but to leave the original dressing, with its inserted drainage, in place so that a drainage track becomes firmly established. After that, the dressings can be changed either daily or every other day for the sake of cleanliness around the outside of the wound; as healing gradually takes place and infection subsides, the drain gradually extrudes and can be cut off a little each day. Finally, the area granulates, and if the exposure is wide, healing can be hastened by secondary suture or by some form of pinch grafts. If a wide area of bone has been exposed, it is sometimes an excellent plan to make perforations over this exposed area down to the diploe, from which granulations spring up and cover the bare bone much more quickly than if the granulating process were allowed to proceed merely from the edges.

Multiple wounds made by small fragments. It has been shown by British neurosurgeons during the present conflict that a very common type of head injury under existing conditions is the spraying of multiple small splinters of bomb casing into various parts of the body, including the head. These splinters are usually quite small, and because of their high velocity are almost red hot when they enter the body. Thus, they are sterile, and such material as may be carried in with them is probably rendered sterile. It has been found that much the best policy with these small fragments is to let them alone rather than to try to extract them operatively. Naturally, the scalp wound should be inspected and may need some

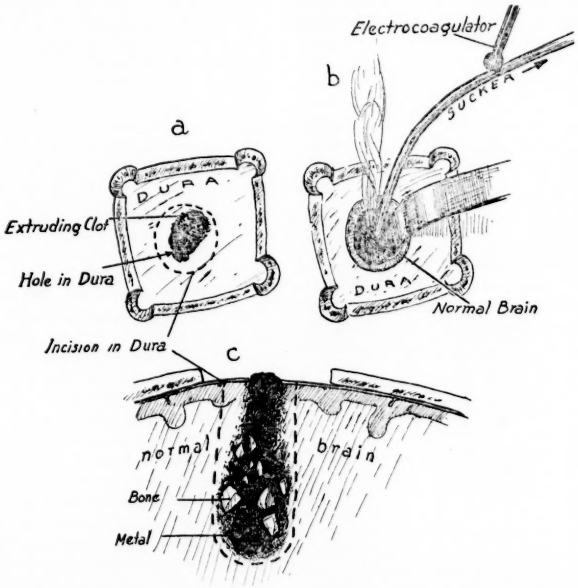

FIGURE 6. *Procedure for Complete Excision of the Contaminated Track of Brain by Electrosurgery and the Suction Apparatus. (Horrax[5]; reproduced by permission of the publisher.)*

Incision of the dura (a) is made outside the track (dotted line), with subsequent removal of the whole area within the dotted line (c), after incision of the cortex just outside the penetrated area (b).

simple form of attention, either simple débridement and closure or perhaps only a simple dressing.

Through-and-through wounds. These wounds are usually made by machine-gun or rifle bullets that have passed from one side of the skull to the other through the brain; they are nearly always immediately fatal, but occasionally the patient survives and enters the hospital in fair condition. Very little need be done to these wounds as a rule. The wound of entrance is small and

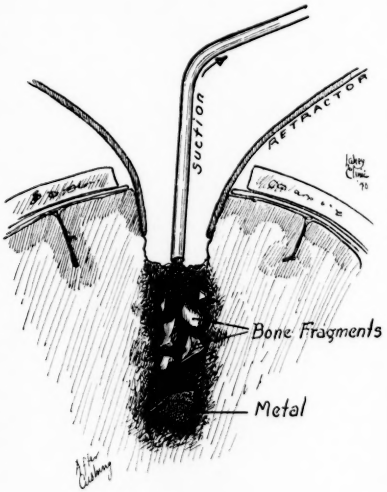

FIGURE 7. *Detail of the Procedure Depicted in Figure 6. (Horrax[5]; reproduced by permission of the publisher.)*

The brain edges are retracted, and the track cleaned out by suction under direct vision.

should be débrided in the usual way to a limited extent, unless x-ray study displays indriven bone fragments that are fairly easily accessible. The wound of exit, which is much larger than the wound of entrance, should be débrided locally, and any loose bone fragments present should be picked out. As in other contaminated wounds, the local use of sulfanilamide or sulfathiazole powder is indicated. If the injury is seen in the early stages, and if the patient is to be kept under observation by the operator, the wound may be closed after débridement, to effect primary union.

Wounds involving the air sinuses. These are extremely serious wounds because, in addition to the compound fracture involving the brain, there is the open sinus, which cannot be closed and which affords a site of continuing infection for a long period. In wounds that have traversed the frontal sinus, the usual débridement of the brain should be performed, as in other types of penetrating wounds. Any general fragmentation of the sinus should be cleaned away as well as possible, such portion of the mucous membrane as has been obviously contaminated or is dirty being removed. If the wound is operated on within the first twelve hours from the time of injury, the dura should be closed, if possible, and the area should then be packed widely open, with gutta-percha tissue or rubber dam against the dura, and with gauze over this for packing. Another method is to close the scalp wound, leaving a drain down through the frontal sinus and coming out of the nose. If such a wound heals by primary union, much time is saved for the patient, but this procedure is far less safe than the open method.

The particular danger present with wounds involving the brain and air sinuses is a cerebrospinal-fluid leak. To prevent this complication, it is imperative, when possible, to close the dura after careful débridement of the brain. If such closure is not possible, a muscle implant may be used over the ethmoid cells when this area has been opened, or a vaseline gauze pack may be placed against the dura and uncovered brain when the wound has involved the frontal sinus. If the wound has been closed either by primary union or by packing off, and if a cerebrospinal-fluid leak develops, the patient must be reoperated on, and the fistulous tract from which the leak is coming sought. This is most frequently just above the cribriform plate of the ethmoid, and this area should then be sealed off with a muscle graft.

Another occasional complication of wounds through the frontal or ethmoid sinuses is the development of an intracranial aerocele. This is caused by the introduction of air through some portion of the dural laceration, and the patient as a rule begins to notice some increasing headache after a sneezing or coughing spell. X-ray study reveals the collection of air in one or the other frontal lobe. This air usually means a fistulous tract between a frontal sinus or the ethmoid cells and the brain. It must be sought and covered with a muscle graft to keep the aerocele from connecting with the ventricle and thus to prevent the development of a cerebrospinal-fluid leak. In all these cases, the continued use of sulfanilamide by mouth is advisable. to offset any possible infection.

Postoperative Complications

Patients who have had serious gunshot or shell wounds of the brain and have been operated on should have their wounds looked at carefully every day for a period of ten days to two weeks or longer if possible. If obvious infection is developing, as shown by puffiness and reddening over the operated area, the wound should, of course, be reopened promptly and left widely open, gutta-percha or some other rubberized type of tissue against the raw brain area being used. It may be wise in some cases to suck out further devitalized material from the superficial portions, at least of the track within the brain, and to treat the track just as one would a brain abscess, that is, by open drainage and by some smooth form of tissue next to the raw brain surface. It is a serious matter when these wounds do not heal by primary union and have to be opened up secondarily in this way, but it is not by any means a hopeless matter, since many of them heal in time with careful treatment; frequently, even a herniation or fungus eventually granulates and recedes and the wound covers over with epithelium in the usual way. When a fungus develops from this source, or when the patient has been operated on late and it is necessary to leave the wound widely open from the start, the fungus should be covered with some smooth material, such as gutta-percha, as stated before, and then surrounded by a doughnut of cotton over which the usual gauze dressing is placed. The doughnut is used to prevent pressure on the fungus, which can only do harm, since it is not possible to keep the fungus from protruding and indeed it is not advisable to try to do so since such protrusion represents an effort of the brain to get rid of pressure. To prevent too great herniation of brain in this way, it may be advisable to do daily lumbar punctures, to reduce the pressure to a certain degree.

Other acute postoperative complications include meningitis and diffuse encephalitis. These can be treated only by keeping the pressure down, so far as possible, by frequent lumbar punctures and by the general use of the sulfonamides, according to the type of organism involved.

Another immediate postoperative sequela, especially in patients who continue to be either drowsy or stuporous for a long time, is the collection of mucus in the air passages. This must be repeatedly cleaned out by suction because if there is not a free airway and if mucus gets down into the bronchial tree, there is every likelihood of an atelectasis or another pulmonary complication. It is imperative to have some form of suction apparatus immediately available on all wards where unconscious or semiconscious patients are situated, because the collection of mucus is a serious matter that must be attended to promptly and frequently.

With the late complications of head injury, such as brain abscess, post-traumatic convulsions, headaches, dizziness and neuroses, this discussion does not presume to deal.

Summary

In the treatment of gunshot wounds of the brain, stress should be laid on such prophylactic measures as can be instituted, particularly the use of tetanus toxoid and of the sulfonamide drugs. The second important feature is the urgent necessity of getting patients quickly to a hospital where complete operative treatment can be carried out for wounds that require such treatment. In general, the earlier these wounds can be treated, the better will be the chance of preventing subsequent infection. Certainly, whenever possible, patients should have their complete operation within twelve hours from the time of injury. No avoidable delay for other purposes can offset the advantages of early operation. Finally, a careful, complete and painstaking débridement of the wound, both of the skull and of the brain, should be carried out, preferably by those who are well trained in this type of surgery.

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WAR NEUROSES*

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WAR neurosis is a three-dimensional problem. Its length can be measured only by time, which reaches from war to war. The casualties of World War I remain a tremendous medical problem, and the effect of the present European conflict is already bringing out evidences of nervous instability in the civilian population. Modern warfare includes men, women and children of all ages. Its breadth encompasses all the neurotic and psychopathic disabilities of civil life and includes practically every symptom in the whole category of medicine. Its height can be appreciated if one studies the report of the Administrator of Veterans' Affairs for 1940,[1] which reveals that 58 per cent of all patients being cared for in veterans' hospitals have neuropsychiatric disabilities. The economic aspect of the problem is appalling when one considers the money spent on training, compensation, pensions, hospitalization and treatment.

The war neuroses begin early. They are long drawn out and difficult to treat, and tend to increase for at least twenty-five years after the cessation of hostilities.

There are three definite points of attack on the war neuroses. First, in the selection of the men who are to enter military service, secondly, in helping to maintain the morale and caring for the mental casualties during combat service and, thirdly, in aiding the soldier during the period of demobilization toward rehabilitation and readjustment to civil life. The problem might well be considered in the light of these three outstanding phases of the soldiers' military experiences: mobilization, combat service and demobilization.

MOBILIZATION

The local draft boards operated in much the same manner in 1917–18 as selective-service boards do today, weeding out the obvious misfits as they came along and depending more and more on the induction boards to make the final decision of fitness for service as time went on. The monotony of the routine examinations became apparent, and medical standards, which were set very high during the early part of the draft, were sustained with difficulty. The induction boards were called on to scrutinize the prospective soldiers more carefully, to eliminate the undesirable ones.

Approximately 3,500,000 men were examined by the neuropsychiatrists at the mobilization centers, and 69,394 were rejected because of some mental aberration. Approximately one third were mentally defective, one sixth were psychoneurotic, one tenth were psychotic, and about the same number were epileptic. The remaining one fourth were inebriates, drug addicts and victims of other neuropsychiatric instabilities. As the war continued and more men became engaged in combat service, the mental casualties increased to a rather alarming extent, and finally a request came from abroad that a more careful selection of men be made on this side before sending them overseas for active service.‡

The physical stresses and mental strains of camp life served as a test for the mental stamina of the soldier, and a screening-out process eliminated many from service overseas. The intimate social contacts of camp life, the arduous military training and the exacting disciplinary measures constituted an experience that was too taxing for certain prospective soldiers to meet adequately. The adaptations that had been built up to civil life began to break down. The men whose intellectual endowments were definitely limited were looked on by their comrades as being stupid, and by their officers as being indifferent. The soldiers were right. But it was the duty of the officers to train these men; hence they were rebuked, humiliated, assigned to kitchen police and other unpleasant tasks and punished; finally, in revolt, they became defiant, went "AWOL," and landed in the guardhouse. Usually, the offenders were seen and examined by the psychiatrist and eventually rejected as being unfit for military service.

It is of interest to note in passing that the psychologic examinations given to groups of perhaps a hundred or more men at one time indicated that intellectually it was the men who fell in the low 10 per cent that made up a large number of the chronic offenders, and it was the high 10 per cent from which many of the noncommissioned officers were recruited. These tests were found to

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 22, 1941.

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‡The following extract is from a cablegram sent by General Pershing[2] on July 15, 1918: "Prevalence of mental disorders in replacement troops recently received suggests urgent importance of intensive efforts in eliminating mentally unfit from organizations of new draft prior to departure from the United States."

give a very adequate measure of the relative intellectual equipment as well as the practical ability of the soldiers, and there was a fairly close correlation between their test scores and their achievements.

There were the shy, sensitive, timorous lads who found the bayonet drills and the practice of "running the dummies through" under the direction of the enthusiastic masters of military technic a bit too realistic, and who became the victims of their own vivid imaginations and undue sensitivity. Some developed physical symptoms, such as nausea, vomiting, fainting, tremors and insomnia; others developed the more serious mental symptoms that are so common in the anxiety states. Some men became morbid and depressed, with definite psychotic symptoms. Every type of mental disorder was precipitated by the inability of the predisposed to meet the demands of camp life. These experiences did not cause the disease; they simply brought an existing instability to the surface where it could be recognized.

Such were the cases that were returned from the camps to civil life or held for noncombatant service. A recognition of these potential neurotics prevented them from developing a more serious mental disability overseas, where the problem of care and treatment would have been tremendously increased.

It is difficult to reconcile the rather superficial neuropsychiatric examinations that are being made at the present time, — limited to about seven minutes for each man, — with the gravity of these casualties both from a military and from an economic point of view. It was recently stated that adequate psychiatric examinations which would weed out the potential neuropsychiatric disabilities would save the Government $500,000,000 for every million draftees.[3] It has been estimated that every psychotic soldier who breaks down in the Army costs the Government $30,000 from the time of the onset of his disease until his death.[4] If psychiatrists can be hired at the rate of $15 a day, it takes but a little mathematical reckoning to determine that if one psychiatrist picked out one potential psychotic every six years, he would save the Government his salary.

Combat Service

The neuropsychiatric disabilities resulting from active military service represent the war neuroses of the American forces of the last war and the shell shock of the British. They are made up of so many and so varied heterogeneous groups that it would be a time-consuming task of but little value to define the limitations of each. In the order of their frequency, and including a very large percentage of all the neuropsychiatric disabilities, they are: neurasthenia, conversion hysteria, anxiety states and the psychoses.

The underlying mechanism of the disability is pertinent to this discussion. The war neuroses represent a group of neuropsychiatric disabilities incurred in military service and resulting, on the one hand, from conflict between acquired social attitudes — such as loyalty, patriotism, honor and the maintenance of one's personal customs and traditions, as well as those of the army, regiment and company, all of which Trotter[5] includes under the term "herd instinct" — and, on the other, from the instinct of self-preservation. These sets of dynamic forces, although always present, are under ordinary conditions not in serious conflict, inasmuch as the herd instinct, or the so-called "social drive," is allowed to operate more or less freely, uninhibited by any interference from the instinct of self-preservation. Only under conditions such as war, floods, earthquakes and panics, in which there is a direct threat to one's existence, does the instinct of self-preservation assert itself and become a dominating force.

The purpose served by the neurosis, as stated, is that of protection, and to be adequate and fulfill the purpose for which it is psychologically designed, the neurosis must protect both the soldier's ego and his physical being — that is, it must permit him to escape from the intolerable situation created by the impending dangers of war on the one hand, and to accomplish this without loss of self-respect on the other.

Since neurosis has been recognized as a medical problem, with symptoms comparable to those of any other illness and since neurosis has been accepted as a medical entity by those in authority, both medical and military, and by the soldier, the public and the press, it has not been difficult for the soldier to accept his disability as a way out of a difficult situation. Consequently, a neurosis solves the conflict between the herd instinct, which drives the soldier on to perform his military duty and to live up to those socially acquired traditions and his personal ideals of what he would like to be, and the instinct of self-preservation, which is constantly threatened by the dangers of pursuing the paths of duty.

It is of interest that neurosis was rarely observed in men at the front or in those who had been wounded and were in base hospitals. However, a certain number of wounded men developed states of anxiety as the time approached for their discharge from the hospital, especially if they were assigned to active military duty.

Neurasthenia, the anxiety states and the psychoses had a fairly equal distribution among all

those engaged in military service — officers and soldiers alike. The so-called "conversion hysterias," however, were found in an overwhelming degree in the more suggestible, less well intellectually endowed soldiers, and were infrequently seen in the officers. These physical manifestations of mental conflict, such as the paralyzed arm or leg, functional blindness, deafness, aphonia, and the more violent tremors and muscular twitchings, represented what might be termed a rather crude method of solving the conflict. In other words, the average soldier confronted with danger met the situation promptly, decisively, and without any great struggle to carry on, whereas the neurasthenic did not. He developed a syndrome with such symptoms as fatigue, insomnia, battle dreams, anxiety and depression, frequently lasting over a period of weeks or months before completely incapacitating him. Many of these men went in and out of the front-line trenches month in and month out until they finally reached the breaking point.

Treatment of the conversion hysterias was usually not difficult. The patients responded readily to methods of suggestion, such as the faradic battery, isolation and hypnosis. However, it was found from experience that as a group they had little to contribute to military service. The other types of cases — the neurasthenias, anxiety states and the compulsive and obsessional neuroses — invariably required long periods of rest and prolonged psychotherapy. It was the experience of the medical officers in the American Expeditionary Force that severe cases of war neuroses that required evacuation to base hospitals were rarely good risks for further front-line service. The origin and purpose of the neurosis is to protect the patient from a situation which he is inadequately prepared to meet because of a poorly organized nervous system and a poorly integrated personality make-up. To return these men to the same situation that created the initial breakdown was a hazardous undertaking. The experiences of the American Expeditionary Force and those of the British Expeditionary Force during the first war were not particularly different from the experiences of the British at the present time.

Debenham, Sargent, Hill and Slater,[6] in a recent article dealing with 1550 cases of neuroses or psychoses in members of the armed forces, state:

> In the early months of the war, cases were largely those men who should never have been regarded as fit for military service. . . . At evacuation of Dunkirk another type predominated, acute anxiety or exhaustion syndromes in men of apparently normal personality, who had not broken down until placed under considerable strain. . . . It is useless to send a man back into army life merely because he is symptom free if he is liable to break down under small strain. An assessment must be made of the personality and of the strains that it is able to support. The longer the neurotic reaction is allowed to persist, the more difficult it is to deal with.

In contrast with American and British attitudes toward the war neuroses, I quote from a book by Martin Gumpert,[7] which presents the German medical and military point of view:

> War hysteria and "trembling" are mere cowardice, masquerading as sickness. It is wrong to cater to war-hysterical people. How then shall the army administration treat them in the future? First, and at once, they must be brought to a war hospital. Their stay in the war hospital will be short and the hospital not too close to home. They must realize that they are to face conditions which will not at all accord with their wishes. Unfortunately, it is not possible, for obvious reasons, to send back to the front men who cannot be cured of their nervousness in the war hospital. Normal men would not understand the reasons why such "poor sick people" should be left in the trenches; morale would suffer. Obstinate cases must be united in special squads and sent to places where they can be put at physical work, without consideration for their nervousness. This work must not be too far from the front, but must be right up in the danger zone — road building, trench work, etc., where the risk is no less great than for the soldiers in the front lines. These men must be forced, without consideration for their neurosis, to those kinds of work which normal individuals might do, because such "trembling" cannot be counted as a sickness. Therefore, war-hysteria, even should it increase, will not be reason enough to remove anyone from the war zone; indeed the strongest pressure must be used upon him to make him fulfill the tasks assigned to him.

It is obvious from American and British experience that the war neuroses as they develop in line of duty represent an extremely difficult type of medical casualty and that therapy should be applied at the earliest possible date not too far removed from the scene of conflict. A fairly large percentage of patients can thus be rehabilitated in a relatively short time and sent back to active service. The cases that do not respond to this type of therapy and require evacuation to base hospitals can usually be rendered symptom free, but it is probably not wise, from a medical point of view, to return the patients to combat service. Many of these men were able to carry on in the Section of Supplies, and rendered a valuable service. However, thousands during the last war (approximately 3000 psychotic and 5000 psychoneurotic soldiers) had to be evacuated to the United States.

Demobilization

It is my opinion that more men suffered from artificially created neurotic conditions during the period of demobilization than from neuroses that developed on the battlefields of France. Literally thousands of men passively succumbed to a life of dependency on the Government and eventually became incapacitated for a self-respecting, independent existence, owing very largely to the oversolicitous service organizations and the unwise distribution of pensions brought about by national sentimentality and political pressure. During the period of demobilization, various national organizations, with the best of intentions, asked soldiers to make claims for disabilities that could by no stretch of the imagination be considered medically valid. It was not for incapacities already existent but in an anticipation of what might possibly occur that many of these claims were made. These men became the unwitting victims of demoralizing subsidies from a paternalistic government.

When men are paid for being sick and penalized for getting well, the medical profession has little or nothing to contribute. The danger of building up a large group of veterans showing pseudoneuroses or compensation neuroses was entirely ignored. There is perhaps no period in the whole experience of military service that is more critical for the future happiness and efficiency of the soldier than this period of demobilization. It is also important to the Government from an economic standpoint, as well as for the preservation of man power. Psychiatry could have contributed much during this period for the welfare of both men and the Government. There was no real need for hurry during demobilization. It might have been an opportunity for carrying out a well-co-ordinated plan for reorienting a certain group of men to civilian life after their war experiences. As history shows, it was anything but that. It could not be done through compensation alone.

Another phase of demobilization that contributed to many maladjustments later on was the hurried, haphazard procedure of placing men in civilian training. Many men were encouraged to take up some form of training for which they were intellectually unfit. Being ambitious, many were lured into attempting to become doctors, lawyers, public accountants, artists and engineers, and into other professions for which their education before or during the war in no way prepared them. They gave up their prewar occupations and lost interest in the pursuits that they were equipped to follow. Failure resulted from the great gulf that existed between their ambitions and their abilities. It is hoped that such obvious mistakes will be eliminated during the next period of demobilization. It is one aspect of the whole situation from which the ex-soldier should be safeguarded.

* * *

In conclusion, I repeat that the war neuroses represent one of the most significant military and economic problems with which the Government has to deal. Every effort should be made to select men with care, to organize medical centers where adequate treatment can be administered during combat service, and to give careful consideration to the problem of rehabilitation after military activities have ceased.

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BLOOD AND BLOOD SUBSTITUTES IN THE TREATMENT OF HEMORRHAGE, SECONDARY SHOCK AND BURNS*

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Successful management of shock requires early recognition and effective measures for breaking the vicious circle. These will be directed toward removing the cause, toward increasing the blood volume and toward relieving anoxia. Saline solutions and artificial colloidal solutions are ineffective or objectionable. Transfusion of whole blood, except after serious hemorrhages, is not advisable. The ideal substance is that which has been lost from the circulation — plasma. Infusions of human plasma or serum should be given when hemoconcentration indicates impending circulatory failure and *before* the arterial blood pressure declines. Oxygen should be given by inhalation to counteract anoxia.

SECONDARY shock may result from extensive operations, from the severe injuries of civil accidents or military wounds, or from burns, severe infections, profound anemias and other conditions.[1] Loss of blood, emotional stress, prolonged exposure to cold, and physical and nervous exhaustion may all be contributing factors. The cycle of deranged function that characterizes the shock state essentially involves injury to and loss of tone of the blood capillaries, loss of fluid and plasma proteins through the capillaries, and tissue anoxia (oxygen-deficiency). Unless this vicious circle can be broken, circulatory failure and death ensue. The mechanisms involved have been well summarized by Moon,[2] who has contributed extensively to their elucidation. The following is quoted from Moon[3]:

> Endothelium is delicately sensitive to lack of oxygen, to metabolic products, cytoplasmic substance, bacterial toxins and to a wide variety of chemicals and drugs. When affected by any such substances, the endothelium becomes relaxed, atonic and abnormally permeable to blood plasma. The sequestration of blood in dilated capillaries reduces the effective blood volume, and the leakage of plasma into tissue spaces lowers the total blood volume. This creates a disparity between the volume of blood and the volume-capacity of the vascular stream bed. This disparity, if not compensated, causes circulatory deficiency.
>
> Compensation is accomplished through responses activated probably by impulses from the carotid sinus. Activity of the sympathoadrenal system causes constriction of peripheral arteries, the discharge of reservoir blood from the spleen into the systemic circulation and stimulation of the heart by the adrenal medullary hormone. So long as the mechanism of compensation is effective there is no marked decline in the blood pressure, but the latter is maintained at the expense of volume flow which is reduced markedly. This stage of shock can be recognized by the presence of hemoconcentration. A progressive decline in the blood pressure signifies that compensation is failing and that the end is near. It is a sign of departed opportunity.
>
> Capillary atony in extensive areas reduces both the total and the effective blood volume and leads to a reduction of the volume flow. This reduces the delivery of oxygen to the tissues. When the supply of oxygen falls below physiologic limits, it augments the capillary atony. Moderate lack of oxygen causes dilatation and hyperpermeability of capillary walls. This effect introduces a selfperpetuating quality which operates as a vicious circle and leads to irreversible changes.

Although there are still points of controversy about the relative importance of the various mechanisms of injury that lead into this cycle of shock, there is general agreement that the critical factor whose correction is the most immediate necessity is the depletion of the volume of circulating fluid. The volume of the circulating fluid must be restored to normal as quickly, and maintained as nearly normal, as possible. For other measures in the treatment of shock, more general discussions should be consulted.[1, 4–7]

For restoring the circulating-fluid volume, intravenous infusions of various fluids made isotonic by diffusible solutes, such as sodium chloride and glucose, have been tried. In general, such fluids offer only temporary relief because of the rapid loss of the added solute from the circulation into the extravascular fluids. Various fluids containing nondiffusible solutes, such as gum acacia, hemoglobin and bovine serum albumin, have been or are being tried. These fluids may have notable advantages from the standpoint of availability and low cost. In general, however, they result in the introduction of foreign substances into the circulation, and no one of them has yet passed successfully through the stage of clinical proof of efficacy and harmlessness. One of these artificial solutions may, of course, ultimately prove to have wide usefulness.

The ideal physiologic corrective for the depleted circulating-fluid volume of secondary shock in man is obviously human plasma or serum. Both plasma and serum have had wide trial in experimental shock (dog serum or plasma being employed in dogs),[4, 8–10] in postoperative clinical shock, and in that following civil accidents, burns or war wounds (human serum or plasma being used).[6, 9, 11] There is general agreement among workers in Great Britain, Canada and the United

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States that either plasma or serum, properly prepared and administered, is an optimal corrective for the depleted circulating-fluid volume of shock.*

There has been a great deal of discussion about the relative merits of plasma and serum for the treatment of shock. It seems that for the purpose of restoring circulating volume there is little difference between them; intravenous infusion of either is efficacious. The advocates of plasma point out that it is possible, by immediate drying of the plasma from the frozen state, to preserve the prothrombin and complement as well as the globulins and albumin of the plasma, and that more plasma than serum can be prepared from a given volume of blood.[11–13] The advocates of serum point out that, since the essential value of the blood proteins in the treatment of shock lies in their colloidal osmotic pressure, the additional preservation of prothrombin and complement has little practical value under the circumstances in question, and that, moreover, serum is easier to prepare and requires somewhat less exacting conditions of administration.

A second point of controversy between the partisans of serum and those of plasma has been with regard to reactions on injection. The consensus seems to be that plasma, either fresh or regenerated after drying from the frozen state, may be given intravenously with no more fear of reaction than in the transfusion of whole blood. Serum that has been aged several weeks before administration or before drying for preservation may be administered with equally little risk of reaction. Some specimens of serum that have been preserved by drying shortly after taking off the clot have caused reactions, but these reactions seem to have been due to special conditions quite outside usual practice in preparing serum.

In current practice, serum and plasma for the treatment of shock are prepared in large pools representing many donors. Such pooled plasma or serum may be administered intravenously without regard to the blood type of the patient.

The question of whether serum or plasma should be concentrated, normal or diluted when administered in shock requires discussion. In general, this decision apparently depends on the condition of the patient; the aim should be to restore as nearly normal conditions as possible. If shock is complicated by concussion, as in accident or war cases, there may be a definite advantage in giving hypertonic, concentrated plasma or serum, which withdraws fluid by osmosis from the central nervous system and tends to restore the circulation to normal.[14, 15] If the patient is markedly dehydrated, a condition that may occur after burns or military wounds, there may be advantage in giving dilute plasma or serum in large volumes. In other circumstances, isotonic plasma or serum may be indicated. Estimation of hemoconcentration or hemodilution by hematocrit readings, hemoglobin determinations or otherwise may afford useful indications of what is required. A rising hemoglobin percentage or an increase of the cells-to-plasma ratio indicates hemoconcentration due to loss of plasma through the capillary walls. When there has been extensive loss of blood, it may be well to follow the immediate treatment of shock by transfusions of whole blood.

It is of course simpler and more economical when practicable to keep plasma or serum in the liquid state. However, under conditions requiring prolonged storage or transportation, as for war purposes, and when concentration is desired, preservation by drying presents great advantages. Drying from the frozen state is generally conceded to be the method of choice, and is the method currently used in the preparation of dried plasma and serum for war purposes.[5, 7]

Several procedures and apparatus currently used for drying from the frozen state have been described under the terms "lyophile," "cryochem"[16] and "desivac."[17] In each of these processes, the plasma or serum is frozen and then desiccated in a vacuum at a rate sufficient to keep it frozen by the continued cooling incident to the loss of the latent heat of vaporization. The three procedures differ essentially in the means used to remove the water evaporated from the material undergoing desiccation. In the lyophile process, the water vapor is condensed as ice in a bath kept cold by dry-ice; in the cryochem process, the water vapor is absorbed by Drierite, a specially prepared, regenerable calcium sulfate desiccant; in the desivac procedure, the water vapor is trapped in the oil of the large vacuum pumps used, whence it is continuously separated by centrifugation. For drying small volumes, that is, up to about a liter daily, the cryochem apparatus has proved to be the most economical in operation, and for larger volumes, that is, from one to many liters daily, the desivac apparatus is the most efficient.

For use in the present war, large volumes of liquid and dried human serum have been and are being prepared in Great Britain. In the months before this undertaking was organized,[18] much liquid plasma was prepared in Greater New York, through the collaboration of the American Red Cross and the Blood Transfusion Betterment Association, and shipped to England. Large amounts

*Concentrated solutions of human serum albumin, now under investigation by Drs. E. J. Cohn and Charles A. Janeway, may prove to have distinct advantages.

of liquid and dried serum are being prepared in Canada for war purposes. Large volumes of dried plasma are now being prepared in this country, with the collaboration of the American Red Cross, for the use of the United States Army and Navy.

For civil use on a small scale, plasma may be prepared directly from fresh whole blood. or plasma or serum may be prepared from blood stored in blood banks until the corpuscles must be discarded. Because of reactions Strumia et al.[11, 12] warn particularly against the administration of fresh (twenty-four to forty-eight hours' old) serum or serum vacuum-dried when fresh; such reactions have rarely been encountered with plasma or with serum held for several weeks in the liquid state before administration or drying. Human plasma and serum prepared by several of the large manufacturers of biologicals have recently been put on the market, but their price is high, owing to the cost of collecting and preparing such products.

Summary and Conclusions

The role of blood and blood substitutes in the treatment of hemorrhage, secondary shock and burns is briefly discussed.

Human plasma and serum are the most effective agents for restoring the volume of circulating fluid to normal in cases of shock and burns, as well as of hemorrhage in the absence of excessive bleeding.

Although serum and plasma are most easily and economically preserved in the liquid form, drying from the frozen state by the lyophile, cryochem and desivac processes is recommended for war purposes and under conditions requiring prolonged storage or transportation.

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MEDICAL PROGRESS

ISOIMMUNIZATION IN RELATION TO INTRAGROUP HEMOLYTIC TRANSFUSION REACTIONS*

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POST-TRANSFUSION reactions of the hemolytic type are most commonly ascribable to intergroup incompatibilities. These accidents have occurred because of mistakes in grouping the blood of the donor or the recipient, and occasionally[1, 2] have been due to the use of a Group O (so-called "universal") donor whose natural isohemagglutinins were unusually potent — that is, effective in high dilution. Probably the commonest error in grouping is failure to recognize persons of Groups A_2 and A_2B because of the low agglutinability of cells containing the A_2 substance. Weak anti-A serums may fail to cause any agglutination of such cells even when unusually sensitive technics are used; consequently, such persons would be mistakenly allocated in Group O or B, and under certain conditions accidents would be expected whether these persons donated or received blood that was actually incompatible.

But in addition to such intergroup causes of reactions, there have been reports of post-transfusion reactions when bloods of homologous groups have been transfused, and when the preliminary tests have been made by experienced observers using potent serums.[3, 4] Reactions under such circumstances have usually occurred in patients who have had repeated transfusions, the first or first few having been uneventful; such reactions have also been observed with unusual frequency following primary transfusions given to pregnant or post-partum women.[5–10] Some recent disclosures coupled with long-known facts afford a plausible explanation of these intragroup incompatibilities. It is the purpose of this review to consider the probable mechanism, which is based on isoimmunization with certain antigenic components of human blood.

ISOIMMUNIZATION

Isoimmunization was successfully accomplished by Ehrlich and Morgenroth[11] as early as 1900. Isohemolysins were readily produced in the goat by injecting erythrocytes of other goats. These immune, not normal, isoantibodies hemolyzed the cells from the goats that furnished the original inoculums and the cells of some, but not all, other goats. The serum did not contain an autolysin — it did not affect or combine with the cells of the animal in which the antibody was formed. These observations were of basic significance in that they showed the possibility that a considerable number of different antigens might exist in similar cells of different individuals in a single species. They also indicated that an animal will not produce antibodies to antigens that are present in his own blood. This principle was expressed concisely by Ehrlich and Morgenroth[11] in the phrase *horror autotoxicus*. It is true that an animal can form antibodies against some of his own proteins or other components of his tissues, for example, the substance of the crystalline lens, casein[12] and an alcoholic extract of brain,[13] but these materials are blood-foreign and thus satisfy one of the primary prerequisites for antigenicity. The preliminary report by Kidd and Friedewald[14] on a natural antibody found in adult rabbits is of interest. This thermolabile antibody, not present in young rabbits, fixed complement strongly in the presence of saline extracts of normal tissues from a rabbit, rat, mouse, guinea pig or chicken. Extracts of liver and kidney were especially rich in the reactive substance. Immune isoantibodies have been produced in other animals and fowls (Wiener[3]).

GROUP-SUBSTANCES A, B AND O AS ISOANTIGENS

Isoimmunization in man cannot, of course, be studied with the deliberate and thorough experimentation permissible in animals, and observations must perforce be limited to cases of inadvertent mistakes in transfusion and to events that may follow or accompany pregnancy when the parents present certain incompatibilities of their bloods. Thomsen[15] did attempt to immunize men by intramuscular injections of incompatible blood, but no significant rise in isoagglutinative titer was observed (one should note the findings of Biancalana and Teneff,[16] however). This apparent evidence against the isoantigenicity of the

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A and B group-substances is, however, outweighed by the positive evidences mentioned below. Thomsen's negative result is probably attributable to the relatively small quantity of blood injected. Possibly, the route of injection had some influence; as an analogy, the report that rabbits treated with suspensions of streptococci produce anti-C much more readily following intravenous than subcutaneous injections[17] may be mentioned.

It is highly probable that the case reported by Thalhimer[18] in 1921 is an example of the isoantigenicity of Group-Substance B. A boy received 300 cc. of his father's blood; cross-matching had revealed no incompatibility, and only a mild febrile reaction ensued. Eighteen days later, without further tests, the father again served as donor; an alarming reaction stopped the transfusion after 150 cc. of blood had been introduced. Subsequently, the bloods were grouped; the son was found to be an O and the father a B. Although no agglutinative titers were determined, one may surmise with confidence that the anti-B normally present in Group O plasma (with anti-A) was too weak to be detected by the ordinary test, and that the primary transfusion of Group B blood served as an immunizing stimulus leading to a probably marked rise in the titer of anti-B, which thus intensified the incompatibility.

Further evidence that A and B are isoantigenic appears in Jonsson's[19] finding that the maternal isohemagglutinins α and β are of higher titer when the corresponding antigen, A or B (not present in the mother's blood), is present in the blood of the fetus than when it is absent (transplacental isoimmunization).

Rø[20] observed the development of immune anti-A agglutinins in a Group O patient given Group A blood. Wiener[21] has recorded 2 cases in which powerful immune anti-B (sixteen times the average titer) was produced; the recipients were O and A, the donors B and AB. Another recent case of isoimmunization of a Group B patient given AB blood is also described in detail. The anti-A titer rose from 1:4 immediately after the transfusion to 1:512 on the eighth day. There was no significant difference in titer whether the tests were done at 37°C. or in the icebox, whereas natural isoantibody as a rule reacts more strongly at low temperature. Prior to this report, the only case of isoimmunity involving these subgroups was the weak "irregular" (a_2) agglutinin found by Landsteiner, Levine and Janes[22] to have developed, or more probably to have increased in titer, following intragroup transfusions. It was slightly less active at 37°C. than at room temperature. A second transfusion from the same donor was not followed by symptoms, although the agglutinin was present after the first transfusion.

Davidsohn[23] has argued logically, principally from circumstantial evidence, that the subdivisions of Groups A and AB — the Subgroups A_1, A_2, A_1B and A_2B — are probably significant in causing some post-transfusion reactions, but direct support of this possible mechanism was lacking until Wiener's[24] report appeared last June.

Wiener has thoroughly analyzed a case of isoimmunization of an A_2 recipient by transfusion of A_1 blood. The a_1 behaved like a "cold" agglutinin. In another case, a_1 antibody was considered to have developed in an A_2 woman as a result of isoimmunization by an A_1 fetus in utero, the general explanation first proffered by Levine and Stetson[5] as the mechanism of reactions following primary intragroup transfusions given intra partum or post partum.

Since these are the only cases of this kind on record, it is clear that these subgroups play a very minor role in transfusion reactions. This is because the vast majority of bloods of Groups A and AB contain neither a_1 nor a_2, and when present the latter are of low potency and are mostly active at low temperature. It seems likely that A_1 and A_2 are feeble isoantigens and produce immune isoantibody only in the rare persons who have some preformed a_1 or a_2. The observations add to the evidence that the difference between A_1 and A_2 is qualitative. Although dangerous reactions are not likely to occur, it is desirable to use donors of homologous subgroups, that inapparent hemolysis may not deprive the recipient of the benefit of his transfusion.

The formation of anti-O isoagglutinin (probably the same as a_2) in low titer has been observed in a Group A_1B patient.[24] The transfused O cells disappeared rapidly from circulation, although the second transfusion of 300 cc. of O blood produced no symptoms.

Type-Substances M, N and P as Isoantigens

Normal isoantibodies for N have never been found; in only 4 cases among several hundreds of thousands of individuals tested has anti-M been detected.[21, 25] Although these three substances, especially M and N, are definitely antigenic in rabbits and other animals, they do not appear to incite the formation of antibody in man. With the exception of a single unconvincing report by Martinet,[27] Type N blood injected into Type M persons, or vice versa, does not produce type-specific isoantibody. Regarding substance P, for which it is difficult to produce immune serums in rabbits, one case is recorded[4] in which an intragroup

(A) transfusion resulted in the development of agglutinins for the donor's blood and for many others of Group A. Further tests revealed that agglutinogen P was specifically affected by this isoantibody.

Rh as an Isoantigen

Last year, Landsteiner and Wiener[28] described an additional agglutinable substance in human blood that was recognized by its reactions with antiserum to rhesus (*Macaca mulatta ?*) blood (hence termed "Rh"). This substance is common, being present in about 85 per cent of the population. Shortly after this discovery, Wiener and Peters[4] studied the bloods of 3 patients who had had hemolytic reactions, one fatal, after repeated transfusions of correctly grouped blood. The serums of these patients contained abnormal isoagglutinins reacting independently of the regular groups and corresponding to the property Rh; their blood cells did not contain Rh. Thus, the conditions for isoimmunization were present. The authors summarize their second case, in the light of the serologic findings, as follows:

> . . . . A patient, group A (Rh–) was given a series of blood transfusions from two donors, one group A (Rh+), the other group A (Rh–). The first transfusion from the donor A (Rh+) gave rise only to a subclinical reaction. The following two transfusions from donor A (Rh–) were perfectly compatible, so that the donor's cells could be demonstrated in the circulation of the patient (with the aid of the M-N tests) for a long time afterwards. On the other hand, the blood from the first transfusion was gradually hemolysed and eliminated, this being accompanied by the appearance of Rh antibodies in the patient's plasma. Later, when a second transfusion of blood from the first donor, A (Rh+), was given, a hemolytic reaction followed. The long interval between the two transfusions from this donor probably allowed time for a fall in the titer of the anti-Rh agglutinins, so that these were not demonstrable either by the hanging drop or centrifuge technic before the last transfusion. The reason why the Rh agglutinins were not demonstrable immediately after transfusion is that they had been completely absorbed by the Rh+ blood introduced into the recipient's circulation. By the fourth day, however, the antibodies had reformed in sufficient amount to be detectable.

Rh+ persons, being about six times as common as Rh–, are that much likelier to serve as donors. The conditions offering an opportunity for isoimmunization would obviously be the transfusion of Rh+ blood into an Rh– recipient. Such transfusions, if primary, would not be expected to result in reactions because normal anti-Rh, which might be present in Rh– persons, has not been found; so, as with M and N, the factor Rh can ordinarily be disregarded in the selection of donors for *primary* transfusions. But an important exception must be well noted. The intragroup reaction reported by Levine and Stetson[5] led them to suggest the ingenious explanation that the fetus in utero is the source of an antigen, foreign to the mother, that gives rise to the production of an isoantibody capable of mediating a reaction to a transfusion of unsuitable blood given during or shortly after pregnancy. In these cases, as well as in repeatedly transfused patients, it has almost invariably been found by Wiener, Levine and their co-workers that the substance Rh is the antigen responsible, the reacting subjects being Rh–.

In such a pregnancy, the usual conditions are that the woman is Rh–, the husband Rh+, and the fetus has inherited the Rh factor from its father. During pregnancy, some Rh antigen from fetal blood (it appears to be absent from other tissues[25, 29]) reaches the maternal circulation from time to time, perhaps through some placental defect, and incites the production of anti-Rh. If the need for transfusion arises, the husband is often selected as donor; he is Rh+ (as are 85 per cent of donors, on the average), and the stage is accordingly set for a hemolytic reaction, which may be fatal. Cross-matching of the bloods by the usual technic may not reveal the incompatibility, and even with the more delicate methods to be described, agglutination may escape detection.[30] Obviously, under these circumstances, and, in general, when one is dealing with patients who have received repeated transfusions, it is prudent to use Rh– donors.

Erythroblastosis Foetalis

Strong corroborative evidence that Rh is an isoantigen of great clinical significance has been furnished by Levine and his collaborators. Levine and Katzin[31] observed that intragroup post-transfusion reactions connected with pregnancy occurred especially in women whose obstetric histories disclosed an unusually high frequency of toxemias, miscarriages and stillbirths. Are these accidents correlated with the presence of irregular antibodies? Studies of erythroblastosis foetalis by Levine, Katzin and Burnham[32] furnished support for this speculation; 6 of 7 mothers possessed an irregular agglutinin corresponding in specificity to anti-Rh. Thus, the pathogenesis of the disease depends on isoimmunization of the mother against blood factors of fetal derivation and the subsequent transplacental passage of the maternal isoantibodies that cause destruction of fetal blood, accompanied by compensatory hematopoiesis.

The predominant role of the Rh antigen is shown in Table 1, which reveals an extraordinarily

high incidence of Rh– in the group of selected mothers, and of Rh+ among the husbands and affected children in these families.[32]

Further evidence of the correctness of the explanation proposed is that a large proportion of the mothers of erythroblastotic infants possess anti-Rh of sufficient strength to be demonstrable in vitro. The proportion diminishes with the lapse

TABLE 1. *Tests Made with Human Anti-Rh Serums.*

SUBJECTS	RH+	RH–
	%	%
1035 persons (general population)	86	14
153 mothers of infants with erythroblastosis	8	92
89 husbands of Rh– mothers	100	0
76 infants with erythroblastosis	99	1

of time after pregnancy — that is, as the period of antigenic stimulation becomes more remote.[29]

In some families, all pregnancies, except perhaps the first, yield infants with erythroblastosis; in others, some of the offspring are normal. Genetically, this difference could depend on whether the Rh property of the father is homozygous or heterozygous. According to Landsteiner and Wiener,[33] the property is inherited as a mendelian dominant and its absence is recessive.* Half the offspring of a heterozygous (Rh+, Rh–) father would be Rh– and thus incapable of immunizing the mother, but if he is homozygous (Rh+, Rh+), all pregnancies will afford an opportunity for the production of anti-Rh. If the first infant is unaffected, it may be because a single pregnancy sometimes does not afford a sufficient stimulus for adequate immunization. Doubtless, mothers as well as transfused patients vary a great deal in the degree of their isoimmunizability as well as in its selectiveness, as the response of animals to heteroantigens does.[36]

Rh– blood is better for transfusing erythroblastotic infants[29, 35]; however, the mother's blood should not be used, since it probably contains anti-Rh. Theoretically, the mother's colostrum might contain a relatively high concentration of isoantibody; perhaps early nursing by the mother should be forbidden.[37]

To explain the few cases of erythroblastosis in Rh+ mothers, one may reasonably assume that the same genetic mechanism is operating but that a different isoantigen is concerned. Antigenic components other than those already mentioned are known to exist in the red cells, and there is no reason to think that still more may not be discovered in the future.

Concerning this particular isoimmunologic disease, such antigens should not be sought in other tissues or fluids if interpretation of past lessons is correct. An early hypothesis was that if a Group B or Group O mother was carrying a Group A child, the mother's α antibody might penetrate the placenta and cause destruction of fetal erythrocytes.[38] However, it could not be shown that such incompatibilities bore any relation to the disease, and it is now known that in most persons the substances A and B are present not only in the erythrocytes but also in various tissue cells and that they are dissolved in various secretions, including the amniotic fluid. This wide distribution allows neutralization of the isoantibodies and serves to protect the fetal red cells. Possibly, those who do not secrete such substances would be less well protected.

An explanation offered by Darrow[39] — that icteric symptoms might be due to an isoimmunity involving differences between maternal and fetal hemoglobins — has not been substantiated. There is, however, a recent report[40] that such antigenic differences do exist and that fetal hemoglobin is more complex than the adult kind; that is, the precipitins in an antiserum for adult hemoglobin are completely absorbed by either antigen, but antiserum for fetal hemoglobin still reacts with the homologous antigen after the precipitins for adult hemoglobin have been completely removed.

EXTRACELLULAR ISOANTIGENS

There has long been considerable speculation[41] about the possibility that incompatibilities may not be restricted to differences between the cellular elements of the blood and the corresponding isohemagglutinins or lysins. A few observations suggest that there may be sufficient isoantigenic differences between the proteins of plasma so that, under appropriate conditions, isoprecipitins or sensitizing antibodies may be formed and may be instrumental in producing allergic shock. In 1916, Marie reported two cases of serum sickness in typhoid patients following a second injection of human serum from typhoid convalescents.[41] Urticarial reactions after transfusions have been described by many authors and are commoner and, usually, severer after repeated transfusions, especially if the same donor is used. Böttner[42] and Traum[43] have discussed this anaphylactic aspect

*The hereditary nature of the Rh factor permits its use in cases of disputed parentage, but only when both mother and alleged father are Rh–, which occurs only once in forty-nine times on the average, so that exclusions based on this factor are rare. However, one has already been found.[28] The putative father and the mother were Rh–, and the child was Rh+. Curiously, — a gross and shameful waste of exclusive evidence, — there was triple proof of nonpaternity (the falsely accused man belonged to Group B, the mother to Subgroup A_2B, and the child to Subgroup A_1B; furthermore, the man and woman were Type M and the child was MN).

Levine,[29] Javert[34] and Katzin[35] have found another atypical agglutinin in an Rh+ mother of an erythroblastotic infant. It reacted mainly with a particular anti-Rh serum. Consequently, the substance detected by this agglutinin may perhaps be genetically related to Rh.

of the problem. György and Witebsky[44] observed a patient who, at intervals of several days, was given a transfusion from the father, a second from the mother, and a third from the father. Symptoms of severe shock after the third transfusion were relieved by epinephrin. The patient's skin reacted to the father's but not to the mother's serum, and the patient's serum fixed complement in the presence of the father's serum but not of the mother's. A similar case of selective cutaneous reactivity is reported by Wiener et al.[24]

Technical Considerations

From the foregoing review, it is obvious that unusually careful precautions must be taken when one is testing for compatibility prior to transfusing pregnant and recently delivered women or any patients who have received previous transfusions. Immune isoantibodies may remain in the circulation for only a few weeks[7] or for more than a year.[29] Wiener and Forer[25] give an example of how extremely complicated the selection of a compatible donor may be. A woman had had chills, fever and jaundice following two transfusions. She belonged to Group O, but her serum agglutinated the cells of each of 28 Group O persons tested. Besides the normal anti-A and anti-B in her serum, there were two abnormal agglutinins, anti-Rh and anti-M. The patient was Rh– and Type N, as would be expected. Inasmuch as one person in five is Type N and one in seven Rh–, it is to be expected that one in thirty-five persons will be N Rh–. Among 90 Group-O donors tested, 2 were found to be ON Rh–. Their bloods did not cause any reaction when transfused into this patient, who entirely recovered.

The necessity of having highly potent serums available for purposes of grouping bloods has been sufficiently stressed.[45–48] It is also apparent that the so-called "universal" donor* does not exist. Even an O Rh– blood containing weak α and β antibodies cannot be safely used in the rare A and A_1B recipients whose serums contain anti-O (a_2).

Considerable difficulty has been experienced in obtaining useful anti-Rh serums, which have been derived from rabbits immunized with rhesus blood,[28] from human beings accidentally isoimmunized,[29] and, very recently, from guinea pigs immunized with rhesus blood.[33] The specific reactivities of different serums are usually but not invariably parallel.[33] This complication may tentatively be ascribed to the existence of subgroups such as Rh_1 and Rh_2. Anti-Rh serums also differ in the thermal range of their activities. Some have the property of so-called "cold" and others of "warm" agglutinins. It would be safest to run tests in triplicate, one in the icebox, one at room temperature, and one at 37°C. For the last, thirty minutes' incubation followed by centrifugation for one minute at 500 r.p.m. is recommended. If, on resuspension of the sediment, no gross agglutination is apparent, the preparation should be examined microscopically.[51]

Technics and general precautions have recently been described in full.[45–48] Inasmuch as the irregular isoagglutinative reactions are much weaker in intensity than those produced by anti-A and anti-B or anti-M and anti-N, it is desirable to use the most sensitive technics possible. Lund's[52] experiments with the regular isoagglutinins show that a noteworthy refinement can be achieved by diminishing the concentration of cells and increasing the quantity of serum used in the test, thus allowing more antibody for each erythrocyte. The usual concentration of cells recommended, 1 to 2 per cent, was found to be excessive and relatively insensitive. A concentration of about 0.06 per cent was eight times as sensitive as one of 0.5 or 1.0 per cent. Concentrations less than 0.007 per cent were thirty-two times as sensitive. Use of these low concentrations involves centrifugation and secondary reduction of the volume of supernate to secure a suitably dense suspension for microscopic examination.

The quality of agglutination in the Rh system is peculiar, being reminiscent of the floccular rather than the granular type observed in bacterial agglutination. Wiener[37] thinks that the Rh antigen may be located partly below the surface of the cell whereas A, B, M and N are superficially located antigens. A new so-called "sedimentative" technic has just been described by Landsteiner and Wiener.[33] Because of the importance of the Rh antigen and the need of further work designed to facilitate its detection, this procedure is described in full.

For the production of the sera large guinea pigs were injected intraperitoneally with a suspension of washed red cells of rhesus monkeys, each animal receiving a dose corresponding to 1 cc., in later experiments to 2 cc., of whole blood. The injection was repeated after five days, and one week later the animals were bled. The sera of the majority of animals were found to show a difference between the two sorts of blood, Rh+ and Rh–, and in a group of ten animals

*A method of rendering "universal" donors' blood safer, by neutralizing α and β, has been proposed by Witebsky and Kleadshoj.[49, 50] The addition of a few milligrams of the isolated A and B substances to 500 cc. of Group O blood suffices to reduce its agglutinative titers to very low levels or to abolish its activity altogether. These writers state that over a hundred transfusions of neutralized Group O blood have been given, mainly to recipients belonging to the other three groups, with satisfactory clinical results even though cross-matching was sometimes omitted. If the expense of isolating the group-substances is not too great, this method may have some usefulness, but it does not remove the need for careful precautions under the circumstances chiefly discussed in the present review, and it would not reduce the danger of transfusing Group O blood into the occasional recipient of Group A or A_1B who has anti-O agglutinins.

usually one or more were found that yielded sera suitable for practical diagnosis. The manner of selecting the sera is given below.

While in the case of the immune rabbit sera the reagent was prepared in the customary way by absorbing the diluted serum with negatively reacting blood, it was found with several guinea pig sera that absorption with human blood resulted merely in a non-specific diminution of the agglutinin content, no matter whether positive or negative blood was used. This led us to test the effect of simple dilution, and indeed it was found that a distinction between positive and negative bloods could be made directly without absorbing sera. (As an analogy, mention may be made of rabbit immune anti-A sera which cannot be specifically absorbed with A_2 cells to produce a reagent for A_1, absorption with A_2 blood serving merely to diminish the agglutinin titer.)

The method for determining suitable sera consists in making serial dilutions by halves and testing with known negative and positive blood. Those sera which show in three (or more) successive dilutions negative reactions with the former and positive ones with the latter blood are usable.

The actual tests can usually be carried out simply by selecting a dilution of the serum, e.g., 1:10, which gives no reactions with negative but definite reactions with positive bloods, those sera that contain appreciable amounts of anti-A or anti-B agglutinins having been

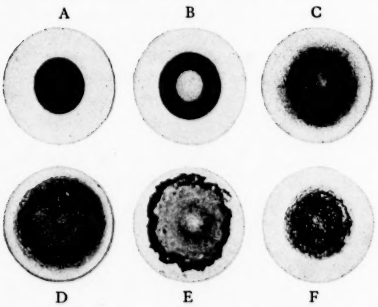

FIGURE 1. *Appearance of Sediments in Bottoms of Tubes. (Reproduced from Landsteiner and Wiener[33] with permission of the publisher.)*

A and B are negative reactions, the inner light disk of the latter being due to a slight convexity in the bottom of the tube; C is a faintly positive reaction; D is a weak reaction; E and F are positive reactions.

previously absorbed with small quantities of A and B blood. Since the sera are used diluted, inactivation is mostly unnecessary. The blood to be tested should be fresh.

Another method, alternative to dilution alone, is to absorb the sera diluted, e.g., 1:4 with a quantity of blood (using A or B cells if indicated) sufficient to remove the reaction with Rh-negative blood.

Two drops (0.1 cc.) of the test fluid are then mixed with one drop of 2 per cent (in terms of blood sediment) washed blood suspension, freshly prepared, in a narrow tube of 7 mm. diameter and allowed to stand at room temperature. Readings are taken after sedimentation has occurred, usually after 30 minutes to 1 hour, by direct inspection of the bases of the tubes, with a hand lens. Negatively reacting bloods then show a circular deposit with a smooth edge, while positive bloods have a wrinkled sediment with a serrated border or show a granular deposit [Fig. 1]. From these readings, as a rule, the diagnosis can readily be made. The readings are facilitated by using racks having small holes beneath the bottom of the tubes. Following the reading the tubes are shaken and the sediment examined after it forms again. A further examination is made after 2 hours, again inspecting the sediment. The tubes are then gently shaken and the suspension is examined microscopically: the negative blood samples are mostly perfectly homogeneous: the positive ones show various degrees of agglutination, not infrequently visible to the naked eye. At times, the clumping is quite weak in spite of a distinctly positive sediment picture. Needless to say, positive and negative control bloods should be included in each test.

As already mentioned, with the great majority of specimens the distinction between positive and negative reactions is quite definite but the positive reactions vary in strength and some bloods offer difficulties because of their weak reactions. However, after sufficient practice, and by repeating the tests if necessary with fresh blood samples and several sera, only in some few instances were the reactions questionable. Marked differences in the intensity of the reactions were also observed in tests made with human anti-Rh sera.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 27481

PRESENTATION OF CASE

A fifty-three-year-old housewife was admitted to the hospital because of jaundice, dark urine and light stools.

About six months before entry, the patient noted the gradual onset of a feeling of "exhaustion," which persisted. Previously, she had been in good health. At about this time, following a "bad cold," she noticed a yellowish tint to the skin. She then began to have from three to five loose bowel movements each day; no blood was passed, however. The patient gradually lost appetite. About seven or eight weeks before entry, there was occasional nausea and vomiting of yellowish material. About a week later, she noticed that her urine became darker and her stools became "putty-like." Her former diarrhea had been replaced by constipation. At about this time, she noted that her skin had again become yellow. From then on, the jaundice continued to deepen. Once, while vomiting, the patient put her hand on the upper part of her abdomen, and became aware of tenderness toward the right side. There was, however, no spontaneous pain until the last few days before entry, when there was a dull ache in the back over the spine of the right scapula. About a week before entry, the patient had some sweating at night, associated with bitemporal headache. She had no chills. On one occasion her temperature was 102°F.

The family and past histories were not of importance. A year before admission to the hospital, a boy boarding at the patient's house developed typhoid fever. Specimens of the patient's blood, urine and stools were therefore examined by the State Laboratory. She was found to be a typhoid carrier, and was obliged to give up her boarding clients.

On admission, the patient was very obese, but was in no acute distress. The skin and scleras were moderately jaundiced. The heart and lungs were not remarkable. The abdomen was obese, with voluntary spasm and tenderness to deep pressure over the upper portion, more marked toward the right. A poorly defined mass was palpable in the right upper quadrant.

The temperature was 101°F., the pulse 95, and the respirations 22. The blood pressure was 96 systolic, 50 diastolic.

Examination of the blood showed a red-cell count of 5,520,000, and a white-cell count of 9200 with 82 per cent polymorphonuclears. The serum contained 9.6 mg. bilirubin per 100 cc., with a diphasic van den Bergh reaction. The serum protein was 6.6 gm. per 100 cc. The prothrombin time was 31 seconds (against a normal of 22 seconds). The hematocrit was 46.8 per cent. The blood Hinton reaction was negative.

The urine showed a ++ test for albumin, with occasional clumps of red and white cells in the bile-stained sediment; it was sterile on culture. The stools showed no pathogens in five successive cultures; on one occasion, an "atypical" colon bacillus was isolated.

The patient was given repeated venoclyses of glucose solution. After the first few days, her temperature remained normal. On the twelfth hospital day, duodenal drainage yielded a small amount of fluid with a bulky sediment that contained numerous red blood cells, occasional clumps of white blood cells and occasional clumps of calcium bilirubinate crystals. There were no cholesterol crystals.

On the thirteenth hospital day, an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. WYMAN RICHARDSON: "She noticed a yellowish tint to the skin." This is important. The question is whether or not there was real jaundice at this time. As we know, patients frequently complain of a yellowish tint that is not due to jaundice. However, in view of the fact that the patient did develop jaundice later, it is perhaps significant in this story.

I might say that I do not see why an operation was performed on this patient in the light of the evidence given here. Realizing that it is very difficult to make these summaries in a brief form, however, I should like to say that one of the easiest tests to perform is that of looking at a stool. As a matter of fact, such a test is one of the hardest things to get done in a hospital. These stools were all sent off and cultured. Whether anyone looked at them, I do not know. I should like very much to know whether the stools were brown or gray.

DR. TRACY B. MALLORY: It is reported that the stools were tan colored.

DR. RICHARDSON: That means to me that some bile was getting through the gastrointestinal tract.

One other thing about the operation: in these

exercises, an operation sometimes includes a peritoneoscopy, so that this patient was not necessarily operated on with the idea of some very radical procedure.

The first question to decide, if possible, is, of course, whether a case of this sort represents intrahepatic disease or an obstruction of the major bile ducts. I believe that the evidence is more in favor of intrahepatic disease than of biliary obstruction. If this had been a case of tumor located at the ampulla or thereabouts, one would expect a progressive increase in the jaundice, which might wax and wane but which should, on the whole, be progressive. Obstruction characteristically produces a severe jaundice frequently associated with severe itching. This jaundice was described by the examiner as moderate, and the van den Bergh reaction corroborates the fact that, although fairly marked, it was not the very severe type that would be seen in complete biliary obstruction. Furthermore, obstruction of the bile ducts by tumor is rarely associated with a febrile reaction, so that I do not believe that this patient had tumor of the biliary tract.

Infection of the biliary tract might account for the fever this patient had; it was not typical of cholangitis, however. A Charcot fever is often associated with real chills. Usually, it runs a short course, and one would not expect it to be relieved by intravenous glucose. That last statement, however, may not be true: the subsidence of fever may not have been due to the administration of glucose; it may have been a coincidence.

The problem of the mass in the right upper quadrant comes into the picture at this point. The abdomen was obese, and the mass poorly defined. Taking these two statements together, in discussing this case, I shall have to assume that there was no mass. The examiner seems not to have been very certain of it. If there was a definite mass, the examiner might have thought that it represented the gall bladder, and an enlarged gall bladder would be, perhaps, slight evidence against the presence of gallstones, according to Courvoisier's law, although that does not hold very much more often than in half the cases. The mass, if there was a mass, might represent some form of tumor in that region and might lend weight to a diagnosis of neoplastic disease. On the whole, the evidence is against an obstruction of the biliary tract, especially low down.

I want to bring up three possibilities, which I wish to discard. The first is the question whether this patient might have had ulcerative colitis, accounting for the diarrhea, because we have seen some patients with ulcerative colitis who developed degenerative liver disease. The cases that I have seen have occurred in patients who had very severe ulcerative colitis and obviously were very ill, whereas this patient, if she had ulcerative colitis, was not sufficiently sick to lead anyone to suspect it and to look for it; so that I think such a diagnosis is unlikely. The question of amebic dysentery comes to mind because of diarrhea and fever, and I wonder if amebic abscesses could produce this degree of jaundice. I think that perhaps they might, but I do not quite see how they could unless there was very extensive disease of the liver. We might just as well rule that out. There is no way of proving it unless the amebas were discovered, and I assumed that they were not looked for. Finally, what bearing did the typhoid bacillus in the biliary tract have on this patient's illness? I must confess that my knowledge of typhoid infection is very slight. Back in 1923, at the time of my first contact with this hospital, we saw four or five cases of typhoid fever during a period of service. I do not recall seeing a case for the past five years. However, if a patient is living with the typhoid bacillus in the biliary tract he would be less likely to have generalized infection as a result of it, having acquired this symbiotic relation. Whether the presence of these bacilli is likely to result in the formation of stones, I am not certain, in spite of the textbooks. On the whole, I believe that the presence of the typhoid bacillus and the fact that the patient was a carrier are probably red herrings in this case.

So far as cholangitis is concerned, I have never been quite sure what cholangitis represents. I gather that it is an infection of the biliary tract that results in jaundice and infection, may be associated with small abscesses in the liver, and may eventually result in a biliary cirrhosis, if the patient does not die first. One should consider cholangitis in this case, but I do not see any suggestion of cholangitis unless we assume that there was obstruction, possibly due to stone, which I have been inclined to rule out. Acute cholecystitis might have been considered, but we must account for jaundice by an acute empyema or infection of the gall bladder. If that were so, we should have to assume that the patient had a stone in the common duct as well as in the cystic duct. Furthermore, I again bring up the fact that the fever apparently subsided after intravenous glucose therapy.

Then, the question of an intrahepatic disease comes up, and I briefly note the patient's symp-

toms. She had a feeling of exhaustion and what was called a cold. She had some apparent infection, followed by diarrhea, then jaundice and fever, with very little pain. It seems to me, taking the whole picture together, that the most likely diagnosis is a toxic hepatitis, with some degeneration or even destruction of the liver associated with fever; when treated in the hospital with glucose, the process might have been held in abeyance.

I should like to emphasize one other point: the blood smear. The patient had a white-cell count of 9000, with 82 per cent polymorphonuclears; this would be consistent with some sort of infection. There was apparently a reduced number of lymphocytes — they must have been less than 18 per cent. If monocytes had been present, there might have been less than 10 per cent, and reduction of lymphocytes could be associated with some lymphoid tumor: lymphoma or Hodgkin's disease of some type. I consider that poor evidence to bring up in favor of lymphoma.

The decision what to do with a patient with jaundice often depends on the course. Here again, I have a right to be a little "peeved" because I do not know the course during the twelve days under treatment, but one gets the impression that the patient was improved. We know that the temperature came down. We do not know whether the jaundice decreased or remained the same. Duodenal drainage was done, but the color of the aspirated fluid is doubtful. I do not know whether calcium bilirubinate crystals are sufficient to give bile color, and shall not take the time to talk about it. I do not consider it important because we have the stool examination. The finding of cholesterol crystals in the bile or the finding of a considerable amount of cholesterol crystals in the duodenal drainage has been considered evidence of gallstones. I am not sure that calcium bilirubinate crystals have the same significance, and on the whole I discard that finding.

To summarize, it seems to me that the course of this disease is that of a toxic hepatitis. I believe that this progressed to a serious degree of actual liver degeneration, and that when this patient was operated on some evidence of a toxic cirrhosis or fibrosis of the liver was found. The operation, I hope, was a peritoneoscopy, because that procedure, in my opinion, might have made a radical operation unnecessary. It is only fair to say that I should assume that the patient, before being operated on radically, would have had more study of the gastrointestinal tract by x-ray or otherwise. She may have been under mosquito bars, and they may not have wanted to take her down to the x-ray room. One other thing: it is true that cholecystectomy has often resulted in the elimination of typhoid bacilli from the stools of carriers, but I assume that this patient was much too sick for operation, on that basis, to be considered.

A Physician: How do you explain the blood in the duodenal drainage?

Dr. Richardson: I might have mentioned that; I considered it quite carefully. One can find numerous red cells from the trauma of passing the tube. We frequently get positive guaiac tests following gastric analysis without a lesion, and therefore I did not believe that one need account for red cells on the basis of an ulcerative lesion. There may have been a bleeding tendency because of a slightly increased prothrombin time.

Dr. Allen G. Brailey: A toxic hepatitis might perfectly well have followed a stone in the common duct with partial obstruction.

Dr. Murray Copeland: I have seen jaundice in association with cholecystitis and no stone.

Dr. Richardson: Due to cholangitis, I suppose.

Clinical Diagnoses

Obstructive jaundice.
Typhoid cholecystitis.

Dr. Richardson's Diagnosis

Toxic hepatitis, with secondary cirrhosis of the liver.

Anatomical Diagnoses

Colloid carcinoma of gall bladder, with direct extension to common and cystic bile ducts, liver and pancreas, and with metastases to peritoneum, ovary, mesenteric and retroperitoneal lymph nodes, mediastinum, kidneys, lung, liver, pleura and thoracic duct.
Icterus.
Ascites.
Hydrothorax, slight.
Chronic vascular nephritis, slight.
Endometrial polyp.
Obesity.

Pathological Discussion

Dr. Mallory: I think one's attitude to the case must depend on how seriously one takes the mass in the right upper quadrant, which certainly was not described in the record as anything very distinct. I gather, however, that the surgeon in charge of the case believed more strongly that there was a mass. At any rate, he decided on an exploratory operation, with the diagnosis of obstruction to the common duct. He did not commit himself as to whether it was due to stone or neoplasm. The abdomen was opened, and an enlarged gall bladder, with walls that were ex-

tremely thick and very hard, was found. In spite of prolonged efforts, the surgeon, and he was a competent one, was unable to locate the common duct. He took a piece of tissue from the wall of the gall bladder and backed out. He also aspirated the gall bladder. It contained some colorless fluid, which was sent to the laboratory for culture. The liver appeared grossly normal except for slight enlargement and bile staining. The patient then pursued a rather rapid downhill course and died in approximately three weeks. The biopsy showed carcinoma of the colloid type, and at autopsy we found a cancer involving the gall bladder, the extrahepatic and intrahepatic bile ducts and the region of the head of the pancreas. In cases such as this, it is sometimes quite difficult to decide at autopsy where the cancer is primary. The possible foci are the gall bladder itself, the bile ducts and the pancreas. In this case, it seemed quite obvious that the pancreas was secondarily involved. The bile ducts, although completely surrounded by tumor and constricted by external pressure, were not invaded or actually occluded, so that I think we can be fairly confident that this tumor was primary in the gall bladder.

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Culture of the gall bladder at the time of autopsy gave a pure culture of typhoid bacillus. Cancer of the gall bladder, we know, almost invariably occurs in patients who have been chronic carriers of gallstones for ten to twenty years. It is the greatest danger of the so-called "silent stone" in the gall bladder. We were therefore surprised to find no gallstones in this case. On the other hand, we have reason to believe that this patient had had a very chronic cholecystitis for many years, owing to the presence of the typhoid organisms. It is at least possible that a typhoid cholecystitis was the long-standing focus of chronic inflammation on which this neoplasm developed. That would be my final interpretation of the case. There was a very slight degree of cholangitis, but the major functional lesion was carcinomatous infiltration around the bile ducts. There were peritoneal implants and also numerous distant metastases.

DR. RICHARDSON: Was any bile getting through?

DR. MALLORY: Bile was still coming down from the liver. It obviously was not passing through the cystic duct, since the bile in the gall bladder was perfectly colorless; however, the bile in the common bile duct and in the hepatic ducts was orange.

CASE 27482

PRESENTATION OF CASE

A sixty-eight-year-old housewife was admitted in a semistuporous, moribund condition.

For about two years, the patient had suffered from "gallstones," occasionally associated with attacks of colic, and at times with jaundice. On the morning before entry, she did not feel well and soon after eating a piece of candy developed an acute, very severe, right-upper-quadrant pain, which tended to travel "down." A few hours later, she began to vomit, and continued to vomit frequently during the night. The pain was intermittent and, despite medication by her physician, persisted until entry.

Thirteen years before entry, both breasts had been removed for cystic disease, and three years later, an operation on the uterus was performed.

Physical examination showed a well-developed and well-nourished, acutely ill woman, who was heavily narcotized. The lips and fingers were cyanotic. There was no icterus. Examination of the chest was negative. The abdomen was moderately distended. There was extreme tenderness, with resistance, across the upper abdomen, and distinct spasm in the right upper quadrant. No masses or organs could be palpated. There was some tenderness below the right costal margin posteriorly and in the right lower quadrant, but it was not so marked as that in the upper abdomen. Peristalsis was heard on only one examination, when there was an occasional rush associated with pain.

The temperature was 99°F., the pulse 105, and the respirations 28. The blood pressure was 120 systolic, 90 diastolic.

Examination of the urine showed a large trace of albumin, a green reaction to Benedict's test and 2 or 3 white cells, many hyaline and granular casts and a few cellular casts per high-power field. The blood showed a red-cell count of 5,100,000 with 86 per cent hemoglobin, and a white-cell count of 10,000. A few hours later, the white-cell count was 6000 with 69 per cent polymorphonuclears. There was a decided polymorphonuclear shift to the left, the majority of the neutrophils being young forms with single lobes.

X-ray study of the abdomen showed no evidence of free gas beneath the diaphragm. There was a large amount of gas in the colon and small bowel, but no definitely dilated loops were seen.

The patient's condition rapidly became worse, the temperature rising within a few hours to 103°F. and the pulse to 150. She died nineteen hours after entry.

DIFFERENTIAL DIAGNOSIS

DR. RICHARD WARREN: This elderly woman died within forty-eight hours of the onset of an attack of abdominal pain which was so severe that it was uncontrollable by several doses of morphine. This pain was due to some "peritoneal insult" in

the upper abdomen, more on the right side than elsewhere. None of the available information is revealing enough to allow me to make a diagnosis that I am confident is correct. Several possible diagnoses suggest themselves, and from these I shall select the one that seems to me the most probable.

The commonest cause of such severe, sudden upper abdominal pain is a perforation of the stomach or duodenum from either ulcer or cancer. There is no history of ulcer or cancer, however (unless one accepts the "gallstone" story as perhaps indicative of one of these), and no subphrenic air was seen by x-ray examination. Moreover, the patient died more rapidly after onset than the usual patient with untreated gastroduodenal perforation.

It is quite certain from the history that the patient had gallstones. The association of jaundice with the attacks of pain supports this very strongly. It is tempting, then, to assume that the terminal episode in the case was some complication of cholelithiasis. The two complications that could give this picture are acute cholecystitis, with perforation, and acute pancreatitis. The former rarely perforates so early in the attack as this, even if complicated by carcinoma of the gall bladder, and is rarely so fulminating. Acute hemorrhagic pancreatitis is a distinct probability. The extreme tenderness across the upper abdomen, the persistent vomiting, the failure of the pain to respond to morphine, the suggestion of tenderness posteriorly and the rapid downhill course all suggest this diagnosis. One would like to see tenderness extending more toward the left upper quadrant than toward the right lower quadrant, but that is not essential.

The only other diagnosis that seems likely is infarction of some intraperitoneal organ, specifically a loop of small intestine. The previous abdominal operation, the abdominal distention, the normal temperature and rising pulse when first seen and, most particularly, the fact that an occasional rush of peristalsis was associated with pain are in favor of this. Against it, however, are the presence of gas in the colon by x-ray examination, and of maximum signs in the upper abdomen at some distance from the abdominal scar and the fact that the physicians in charge did not consider this diagnosis seriously enough to operate.

The only point in the case that makes one somewhat suspicious that the sole diagnosis was pancreatitis is the fact that at two places in the case summary it is intimated that the process tended to spread to the right lower quadrant. This suggests a leak of some septic or irritating fluid down the right gutter. This is possible in pancreatitis, and may represent fat necrosis. It would, however, be more likely in duodenal or cholecystic perforation.

Clinical Diagnoses

Perforation of gall bladder.
Peritonitis.
Acute cholecystitis.

Dr. Warren's Diagnoses

Cholelithiasis.
Acute hemorrhagic pancreatitis?
Perforation of the gall bladder?

Anatomical Diagnoses

Acute hemorrhagic pancreatitis.
Acute aseptic peritonitis.
Multiple fat necroses.
Bronchopneumonia.
Cholecystitis, chronic.
Cholelithiasis.
Operative scars: bilateral simple mastectomy; appendectomy; ventral suspension of uterus.

Pathological Discussion

Dr. Tracy B. Mallory: Dr. Warren was able quickly to narrow down the differential diagnosis to two possibilities: perforation of the gall bladder and acute hemorrhagic pancreatitis. It is evident that the clinicians on the ward also went through an essentially similar process of reasoning, but as their first choice they picked perforation of the gall bladder. The post-mortem examination proved that Dr. Warren was correct. When the abdominal cavity was opened, considerable amounts of slightly turbid fluid were found in which were numerous droplets of fluid fat. All the peritoneal surfaces were studded with small chalky foci. When the gastrocolic ligament was incised, the anterior surface of the pancreas presented as a swollen, purplish mass. Incision into the organ demonstrated many spots of chalky fat necrosis and also many semiliquid foci of hemorrhagic necrosis. As is almost always so in hemorrhagic pancreatitis, there was a diseased gall bladder. Its walls showed fibrous thickening. It contained turbid fluid with but little color and eighteen small, rather friable gallstones. The hepatic and common bile ducts were normal, and there was no stone at the ampulla. The remainder of the autopsy showed little of interest. There was minimal aortic and coronary sclerosis and bare traces of incipient bronchopneumonia.

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HIDDEN HUNGER

Mass starvation requires time before its full impact is felt. The past winter in Europe, devastating as it must have been, did not produce the degree of physical injury that was feared. Populations might have been in the process of starving, but they had not starved; the fatted calves had been rerouted into Germany, but bellies could still be filled with the husks that the swine had left; epidemics of disease were anticipated, but they did not materialize.

Dr. Harold C. Stuart, of the Harvard School of Public Health, recently spoke to the American Academy of Pediatrics concerning some of his observations in visiting unoccupied France this year. The people there, and particularly the children, were not, apparently, so poorly nourished as had been expected; certainly, they were in much better condition than those of Spain, through which country the party had traveled into France. However, in those cases in which vitamin levels of the blood were determined, the significant fact was brought out that these levels were low, occasionally to the point of depletion.

At the same meeting, Surgeon General Thomas Parran, of the United States Public Health Service, elaborated on the distinction between the "hollow hunger" of empty starvation and the "hidden hunger" of vitamin, mineral and protein deficiency. Hollow hunger can be mitigated from time to time by the husks of food with which the belly may be filled; hidden hunger gnaws relentlessly on, sapping the strength, the vitality and the ambition of its victims.

Hidden hunger is the inexpensive, scientific weapon with which Germany can and will hold whole nations in subjection once they have been conquered by the sword. An adequate diet is the weapon with which we, as a nonbelligerent (if not a silent) partner, must make sure that we adequately equip our allies. A country that a few short years ago was ploughing under its wheat, burning its potatoes and killing off its hogs may soon be forced to step up its production and even ration such critically important food supplies as meat, cheese, eggs and milk, that the unconquered democratic countries may maintain their vigor, their initiative and their resistance.

This task and this sacrifice are up to us. We are still living in a land of plenty, but we may yet have to tighten our belts if those nations with which we have thrown in our lot are to achieve eventual victory, or even, perhaps, remain unconquered.

GOLDEN JUBILEE

Another milestone in the progress of "quality-milk" production was passed when, on September 17, the Walker-Gordon Farm at Charles River Village, Massachusetts, celebrated its fiftieth an-

niversary. At that time, the World's Fair rotolactor was officially dedicated. A few weeks later, the fiftieth anniversary was further celebrated at the Walker-Gordon Farm at Plainsboro, New Jersey, where the original rotolactor has been in service for several years.

Although certified milk and Walker-Gordon have been associated in our minds for years, so that the terms have seemed almost interchangeable, the two developments, directed toward the same purpose, appeared spontaneously and independently. Walker-Gordon started producing what was probably the world's first really clean milk in 1891 in Massachusetts; Dr. Henry L. Coit, of Newark, New Jersey, conceived the idea of the medical certification of certain dairy farms in 1893, and, the first farm to be so certified was in that state.

The certification of farms physically equipped to produce pure milk and managed by farmers intellectually and morally equipped for its production has been the most powerful motivating force for improvement that the milk industry has ever received. Today, however, certification or noncertification is not so important as the facts that knowledge of the requirements of clean milk production are well known, the way having been shown by certified milk, and that, by and large, the certified farms still fulfill these requirements.

Walker-Gordon Farm, which antedates certification, has long served as a model certified dairy, as well as a research laboratory for the scientific improvement of milk production and the modification of milk for infant feeding. Here, vitamin D milk was first produced on a commercial scale, and many improved methods of laboratory control were developed; at the Plainsboro farm, the forage dehydrator, a conserver of vitamin A, first came into use.

The installation of the rotolactor, making a complete inexorable revolution every ten minutes, with its constant procession of disciplined mammals, furnishes a token that Walker-Gordon is looking forward to another fifty years of progress. Six prize bulls, serving numbers of selected cows by artificial insemination, are a guarantee that good milking stock will be perpetuated.

MEDICAL EPONYM

Islands of Langerhans

These structures are described in an inaugural dissertation submitted in candidacy for the degree of Doctor of Medicine from the Friedrich Wilhelm's University at Berlin on February 18, 1869, by Paul Langerhans (1849–1888), entitled "Beiträge zur mikroskopischen Anatomie der Bauchspeicheldrüse [Contributions to the Microscopic Anatomy of the Pancreas]." This monograph was privately printed by Gustav Lange, of Berlin, in 1869. A portion of the translation follows:

> These cells are small and irregularly polygonal in form; their contents are quite homogeneous, glistening and without granules; the nuclei are clear, round and of medium size. Their average diameter is from 0.0096 to 0.0120 mm., and that of the nuclei from 0.0075 to 0.0080.
>
> These cells for the most part lie in clumps, peculiarly distributed in the parenchyma of the gland. If a pancreas that has been in Müller's liquid for two or three days is examined under low power, such as No. 4 objective in Hartnack's system, there will be observed regularly scattered in the gland rounded spots stained a deep yellow, about one to a field when a No. 3 ocular is used. Under higher powers, it is evident that these spots consist entirely of our cells. They are heaped up in rounded clumps, regularly distributed in the parenchyma (in the old meaning of the word) of the gland. The clumps have for the most part a diameter of 0.10 to 0.24 mm., and can easily be perceived even in teased preparations made either from fresh glands or from those that have been treated for a short time with iodine serum.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

SECTION OF OBSTETRICS AND GYNECOLOGY*

Fatal Lobar Pneumonia in Pregnancy

A thirty-six-year-old primipara who had had no care whatever was seen, when about eight months pregnant, by her family physician, who immediately referred her to the hospital with a diagnosis of lobar pneumonia.

The temperature was 103°F., the pulse 130, and the respirations 32. Physical examination showed a well-developed woman. The heart was not enlarged; there were no murmurs. The entire left lung was consolidated. The pulse was rapid. The uterus was enlarged to a size consistent with an eight months' pregnancy. The general physical condition was very poor.

Two days after admission, the patient started in

*A series of selected case histories by members of the section will be published weekly. Comments and questions by subscribers are solicited and will be discussed by members of the section. Letters should be addressed to Dr. Raymond S. Titus, *Secretary*, 330 Dartmouth Street, Boston.

labor and delivered herself spontaneously of a stillborn infant. She died the following day.

Comment. Pneumonia has always been recognized as a very serious complication of pregnancy. This death occurred before chemotherapy in pneumonia had been established, and although chemotherapy might have influenced this outcome, it is very doubtful whether the result would in any way have been changed after the patient was seen. This death can be attributed either to neglect or ignorance on the part of the patient. Why the patient had not consulted anyone is not clear from the record. Probably, her economic status had much to do with this, although prenatal clinics are available for those who cannot afford their own physician. It is essential that patients who are pregnant, particularly in the later months, be warned about the seriousness of the common cold and that they be advised to have medical attendance immediately. In this way only may pneumonia sometimes be averted, and in this way only may chemotherapy be instituted soon enough to be of value.

As is very common in serious cases of pneumonia during pregnancy, this patient delivered herself spontaneously of a stillborn infant after a short labor. Recoveries do occur in some patients who seem desperately ill and whose uteri are spontaneously emptied, probably because the load on the heart is lessened and the lungs are given freer space for expansion. It is an obstetric axiom, however, that artificial induction should never be attempted.

MISCELLANY

PREVAILING INFECTION RATE OF TUBERCULOSIS

The mortality from tuberculosis has been quartered in forty years. This fact, however, reveals no accurate information regarding prevailing infection and morbidity rates. That they are less is too logical a deduction to be doubted, but their decline relative to that in mortality has been a matter of conjecture. The following report on autopsy findings (Landé, K. E., and Wolff, G. Frequency of tuberculous lesions at autopsy. *Am. Rev. Tuberc.* **64**:223–239, 1941) throws valuable light on this question, especially since accurate studies extending over the past half century furnished the needed controls for comparison.

In 1900, Naegeli published a careful report of 508 autopsies. Of the adults over eighteen years of age, 93 per cent showed healed, inactive or active tuberculous lesions in the lungs. Only 17 per cent of those under eighteen yielded positive findings. Other investigators substantiated these findings, and in the early years of this century the belief was prevalent that all adults had at some time suffered an invasion by the tubercle bacillus.

Opie as late as 1917 found positive evidence of infection in all of 50 autopsies on adults and in nearly 24 per cent of a group of 93 children, the latter showing a far higher figure in the adolescent years. These findings led Opie to remark, "Almost all human beings are spontaneously 'vaccinated' with tuberculosis before they reach adult life."

In 1922, Wason reported positive findings in 82 per cent of his autopsies, and in 1925 Lambert and de Castro Filho reported a rate of 72.8 per cent in a large series from Brazil. As late as 1927, Todd still found evidence of tuberculous infection in 69 per cent of autopsies done in Edinburgh on patients who had died of some cause other than tuberculosis. Such evidence indicates rather clearly that the decline in infection rate has not kept pace with the mortality from this disease.

The present study was carried on at the Washington County Hospital in Hagerstown from September, 1938, to August, 1940, all autopsies being performed by the same pathologist. There were 176 autopsies during this period, which represented 45 per cent of the deaths that occurred. Eleven of these were rejected because they were not complete post-mortem examinations, leaving 165, which are included in this report. Cases of active tuberculosis are not admitted to the hospital. The population of Washington County is semirural, and most of the patients were long residents, from all classes of society and of the white race (there were only 4 Negro adults in the group).

Thirty-two of the 165 necropsies were done on children, and 133 on adults. For the whole group, positive findings were recorded in 65, or 39.4 per cent, which is just half of Naegeli's findings, 79.9 per cent, when he included all ages.

Considering only the adult group of 133 cases, the positive evidence of infection yielded 47.4 per cent, again strikingly near half the number of adults found to be infected by the earlier researches of Naegeli, Burkhardt, Opie and others. In this series, there were 5 cases in which infection was suspected but could not be proved pathologically. If these are included, the percentage stands at approximately 50.

This finding of almost 50 per cent of positive tuberculosis among an unselected group of semirural population indicates that the frequency of tuberculosis is still sufficient to be alarming. If one assumes this experience as typical of the country as a whole, which seems reasonable, one must still face the fact that at least half of all adults have suffered invasions by the tubercle bacillus active enough to leave discoverable scars. This is disconcerting in face of the far greater fall in the death rate from the disease.

At the same time, there is some compensation in the discovery revealed by this study that only half as many people who have suffered tuberculous infection actually die of the disease as died forty years ago. The infection rate has been reduced to 50 per cent, and the mortality to 25 per cent of that in 1900. A number of factors have probably contributed to this gratifying preponderance in the decline of the death rate. Better sanatorium care and the management of cases have undoubtedly made a large contribution. The fact that lessening of the infection rate has apparently shown acceleration in the past fifteen or twenty years brings comfort to those engaged in both the preventive and the therapeutic aspects of tuberculosis control. A 50 per cent reduction in the reservoir of spreaders must certainly mean that fewer contact cases are today submitted to massive and repeated doses of infected material. The contribution of compression therapy and surgery to this result can but be inferred. Those who advocate freer use of these measures certainly would

seem to have little for which to apologize in the evidence presented by this study.

However, other factors in the picture, perhaps, deserve first mention. Isolation is the time-honored scheme for the control of epidemic, infectious disease. It is a significant coincidence that during the period when tuberculosis mortality was reduced to one quarter its 1900 level and the infection rate cut by 50 per cent, the sanatorium beds in this country increased from about 6000 to 100,000. It would be idle not to recognize this prophylactic procedure as an outstanding influence in lessening opportunity for infection among the general public.

The result of this procedure would have been far more striking had it been possible to arouse the medical profession to its responsibility in finding the early case and effecting its immediate isolation. Unfortunately, this is one of the weaker links in the control program. From three quarters to four fifths of all patients admitted to sanatoriums are still found to be in the advanced stages of the disease, already probable spreaders of the infection to others. More professional education, both undergraduate and postgraduate, is still needed to impress on physicians how truly further progress in tuberculosis control rests in their hands.

Popular health education and school hygiene have also played their parts in reducing opportunities for infection. Beginning with teaching the infectivity of sputum, the transference of disease through common utensils, uncleanliness in restaurants and the menace of infected food handlers, instruction has proceeded to the point where even an open case is of relatively little danger to the patient's fellows if both he and they exercise the prophylactic measures now recognized as largely effective.

Finally, better housing, elimination of industrial hazards, more applied knowledge of the laws of nutrition and a growing consciousness of the significance of personal and community hygiene have played their part in reducing the transmission of tuberculous infection from case to contacts.

A highly significant factor in this study is the observation that reduction of infection as shown at autopsy has been at least as rapid among infants and children as among adults. These younger members of society can make no personal contribution to their own protection. They must rely on that of others — nurses, teachers, parents and relatives. Cutting their infection rate in two, as well as that of their elders, is clear proof that a better-informed public is making an increasingly effective fight against spread of this disease.

Frost, in discussing the eradication of tuberculosis, wrote as follows:

> Tuberculosis also differs from the other directly transmitted respiratory tract infections in that its mortality has declined consistently for the last fifty years or more and continues to decline in every part of this country for which adequate statistics are available. It is not directly established by comparable statistical evidence that there has been a proportionate decrease in the prevalence of infective cases of the disease, taking into consideration not only the number of cases but duration of the open stage. However, there appears to be no good reason to doubt that the prevalence of open lesions effective in spreading the tubercle bacillus has diminished progressively, and continues to diminish in each considerable period of time.

However, it must not be overlooked that, according to present autopsy records, the reservoir of adults infected with tuberculosis at one time or another in their lives still amounts to half the population. Therefore, tuberculosis can still flare up again whenever external conditions turn to the worse for the bulk of the people. Without such a reverse, there exists the hope that further efforts in the campaign against tuberculosis will some day lead to a complete eradication of the white plague. — Reprinted from *Tuberculosis Abstracts*, November, 1941.

NOTES

Twenty-three appointments to the teaching and research staff at the Harvard Medical School, effective during the present academic year, were recently announced as follows: assistants in medicine, Theodore B. Bayles, of Jamaica Plain, M.D. Harvard '36, L. Tillman McDaniel, of Denison, Texas, M.D. Harvard '36, and Thomas A. Warthin, of Boston, M.D. Harvard '34; research fellows in medicine, Charles C. Bailey, of Boston, M.D. University of Virginia '37, Ephraim P. Engleman, of Cambridge, M.D. Columbia '37, Cutting B. Favour, of Washington, D. C., M.D. Johns Hopkins '40, Abraham S. Freedberg, of Newton, M.D. Rush Medical College '34, Harry F. Klinefelter, Jr., of Baltimore, M.D. Johns Hopkins '37, Julian E. Levi, of Boston, M.D. Johns Hopkins '38, Philip S. Owen, of Chester, Connecticut, M.D. Yale '37, and James V. Warren, of Columbus, Ohio, M.D. Harvard '39; research fellows in surgery, Rutledge W. Howard, of Jersey City, New Jersey, M.D. '37, and John E. Adams, of Brookline, M.D. Harvard '39; research fellows in physiology, Douglas D. Bond, of Cambridge, M.D. University of Pennsylvania '38, Robert Galambos, of Cambridge, Ph.D. Harvard '41, and Manoel da Fronta-Moreira, of Rio de Janeiro, Brazil, M.D. National School of Medicine, Brazil, '40; assistants in ophthalmology; Franklyn D. Burger, of Wellesley Hills, M.D. University of Michigan '36, and Thomas J. Cavanaugh, of West Roxbury, M.D.C.M. McGill '35; research fellows in pharmacology, Enrique M. de Espanes, of Cordoba, Argentine, M.D. University of Cordoba, Argentine, '28; teaching fellow in anatomy, Gabriel W. Lasker, of Brookline, A.M. Harvard '40; assistant in pediatrics, Winthrop I. Franke, of Jamaica Plain, M.D. Harvard '38; research fellow in biological chemistry, Thomas R. McLin, of Peoria, Illinois, M.D. Western Reserve '39; research fellow in legal medicine, Herbert S. Breyfogl, of Brookline, M.D. University of Chicago '37. In addition, Norman Weissman, of Boston, Ph.D. Columbia '44, was appointed a research fellow in dental medicine.

Dr. Frederic A. Gibbs, of Boston, was recently given one of the two annual Mead Johnson Awards by the American Academy of Pediatrics for his contributions to present-day knowledge of epilepsy.

Twenty-one Charles Hayden Memorial Scholarships were recently awarded to members of the first-year class at Tufts College Medical School. These scholarships are made possible through a gift of $20,000 by the Charles Hayden Foundation, and they are awarded on the basis of financial need to young men who intend to enter the general practice of medicine. The recipients were as follows: Ward A. Albro, Winchester; Frank A. Avola, Boston; George R. Bancroft, Jr., Winchester; Louis Burke, Chelsea; Joseph L. Cafarella, Malden; Robert C. Cornell, Mountain Lakes, New Jersey; Brendan F. Crotty, Jamaica Plain; Albert A. Delery, Somerville; Gordon N. French, Newton Center; Leon Herman, Brighton; Francis D. McCarthy, Chelsea; David E. McGaw, Winthrop; George B. McManama, Waltham; Stanley J. Mikalonis, South Boston; Edward S. Murphy, Jr., Belmont; Morris Supo-

witz, Chelsea; John DeV. Sweeney, Waltham; George J. Tsolas, Watertown; George L. Tully, Jr., West Newton; Lansing P. Wagner, Cambridge, and William J. White, Jamaica Plain.

CORRESPONDENCE

"INTERN SUPPLY AND DEMAND"

To the Editor: The editorial in the October 2 issue of the *Journal* concerning "Intern Supply and Demand" contains assumptions both expressed and implied which we believe warrant discussion.

It is stated, "Even if medical schools could increase their output and thus satisfy the demands for intern service . . . this merely means that a serious oversupply of practicing physicians would eventually occur, since the very increases in the utilization of hospitals that brought about the present disproportions have already diminished the practice of domiciliary medicine." Though we may be mistaken, it appears that this statement points out that the field of private practice is growing smaller and, therefore, that the graduate output should be at a relatively fixed number, which in fact has been maintained for the past ten years. Yet it also recognizes that hospitals have been meeting a larger and larger medical need, both absolutely and relatively, in the community. It is evident, and the editorial expressly agrees, that the policy of a fixed supply of medical graduates must mean, in general, inadequate medical care where at present the greatest need exists. What should be done about this problem? To discuss it by deploring unfair competition among hospitals for interns and by warning the unwary intern against financial lures of inferior hospitals hardly seems adequate.

Whose needs should decide, in all fairness, the yearly number of medical graduates: the demands of organized medicine for a safeguarded private practice or the actual changing medical needs of the entire community? The editorial appears to imply that the yearly supply of medical graduates must be determined by the opportunities for the private practice of medicine. Yet one must agree that this criterion is hardly satisfactory if it prevents adequate care of the sick. In fact, an attempt to safeguard private practice at the expense of adequate care may well result in a dissatisfaction that will shorten the road to governmental medicine.

We should squarely face the problem of the community's need, which is, more physicians in hospitals. Is it not conceivable that if the number of physicians in hospitals bore a more reasonable relation to the increasing demands of the community on the hospitals, the present number of physicians would be more nearly adequate to the demand made on medicine? The problem, therefore, is not how to limit the number of medical students, but how to induce physicians to stay in the hospitals beyond the ordinary internship period.

The answer must be looked for in the reasons why interns leave the hospital. The intern's life as a rule consists of overwork, poor food and dependence or poverty. The present shortage of interns means increasing routine laboratory work and therefore steadily deteriorating educational opportunity in the internship. For a proper medical education, a longer period of hospital work is now necessary. This prolongs the individual's dependence. The long training period is extremely expensive, and as Dr. Alan Gregg, of the Rockefeller Foundation, has recently pointed out, this means that medical graduates are being drawn from an increasingly restricted financial group of society. This is hardly an intelligent or a democratic procedure, and Dr. Gregg has suggested the subsidization of medical training as a remedy. Furthermore, recent advances in medicine have shown that, in every field, a man must have the fundamental satisfactions of life. This is the more true for physicians, who have to deal with tremendous numbers of patients who have failed in attaining some of these satisfactions. The blind cannot lead the blind! It follows that the medical graduate is in urgent basic need of a home, wife, children and financial independence. Is it any wonder, then, that medical men now yield unquestionably to the financial and other rewards of private practice?

It is obvious, therefore, that to induce physicians to stay in the hospitals, where they have to be to meet the needs of the community, the present setup will have to be altered fundamentally to permit them to lead normal lives as soon after graduation as possible. The Oslerian tradition of monasticism in medicine is incompatible with the demands of the modern physician. Nor does the easy statement of the older clinician, "It wasn't like that when I was an intern," get us very far; he has forgotten that he used to travel by horse and buggy, which he was delighted to see disappear.

We have spoken with many interns and resident physicians about the matters discussed in this letter. They agree that the points raised are well worth discussion from the point of view of the medical needs of the community, of enlightened medical practice, of the intern and of the practitioner.

A Group of Resident Physicians

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In the editorial, space was necessarily limited, and the *Journal* is very glad to print further discussion. The names of the six residents who signed the letter have been omitted, at their request.

In considering the problem, one should bear the three following thoughts in mind: the fixed number of medical graduates represents the greatest possible output of American medical schools unless their present facilities are enlarged or their present educational standards are lowered, or both — whether it is the optimum number and why are other matters; it is also a fact that the community must absorb and support the yearly supply of medical graduates — whether it does so through the channels of hospital, domiciliary, public or private care is a secondary matter, and will eventually be determined by the laws of supply and demand; and the disproportions that are now apparent between the supply of and the demand for interns need correction, which was the reason that the subject was brought up for discussion.

The most immediate corrective measure would appear to be a lengthening of the years devoted to hospital practice, thus shortening those subsequently devoted to extramural activities, with whatever financial or other adjustments are available or obtainable therefor. Other, and perhaps more effective, corrections are no doubt possible. These must naturally be made in the interest of the recipients of medical care rather than in that of any group of its dispensers. Ed.

Erratum

In a letter by Dr. George Saslow published in the November 6 issue of the *Journal*, the word "no" was inadvertently omitted from the first sentence in the second paragraph. The sentence should read as follows: "It might be thought that *no* special attention need be given

these points in the northern part of the United States, but this is apparently not so."

BOOK REVIEWS

Textbook of Pediatrics. By J. P. Crozer Griffith, M.D., Ph.D.; and A. Graeme Mitchell, M.D. Third edition, revised and reset. 8°, cloth, 991 pp., with 220 illustrations and 66 tables. Philadelphia: W. B. Saunders Company, 1941. $10.00.

In this, as in previous editions, the wide range of pediatric interest is covered with remarkable thoroughness when one considers the limitation of space imposed by a single volume. The new edition has been entirely rewritten, and the first portion, which deals with growth and development, has been materially enlarged. This is the field in pediatrics that the general practitioner who graduated several years ago will find particularly useful.

It is difficult not to deal in superlatives in considering this book, which can be unqualifiedly recommended both to students and to practitioners of medicine.

It is a tragic circumstance that since the book was written both the authors have died — Dr. Griffith on July 21 and Dr. Mitchell on June 1, 1941. This third and final edition by these two eminent pediatricians is therefore especially significant.

Hutchison's Food and the Principles of Dietetics. Revised by V. H. Mottram, M.A. (Cant.), and George Graham, M.D. (Cant.), F.R.C.P. (Lond.). Ninth edition. 8°, cloth, 648 pp., with 30 illustrations. Baltimore: Williams and Wilkins Company, 1940. $6.75.

The ninth edition of this well-known book is a welcome addition to medical literature. The original volume was first published in 1900, so that in forty years not only have nine editions been issued, but each edition has been many times reprinted. It has become a standard book on the subject, in both Great Britain and this country, and is a lasting monument to Sir Robert Hutchison, who originally compiled the material and gave the medical profession one of the outstanding books on the scientific aspects of nutrition and the treatment of diseases.

There have been changes in the knowledge of nutrition, particularly in relation to vitamins, since the eighth edition was published. In addition, the world has become conscious of the value of foods, not only in the treatment of disease, but in the general welfare of populations, particularly in relation to war conditions. Wartime has always proved an incentive to the study of dietetics, and the present era is no exception to this rule. The new edition of this book considers the more recent advances in the nutritional field.

Hemorrhagic Diseases: Photo-electric study of blood coagulability. By Kaare K. Nygaard, M.D. 8°, cloth, 320 pp., with 59 illustrations. St. Louis: The C. V. Mosby Company, 1941. $5.50.

This book represents a serious attempt to study the mechanisms of blood clotting by the use of a photoelectric technic. A "coagelgram" is obtained by photoelectric scanning of the clotting of recalcified plasma. To the reviewer, the detailed descriptions of the various steps in the clotting process, as mechanically observed, are of less interest than the excellent reviews of the literature and the discussions of the nature of the coagulation problem. It cannot be denied, however, that the introduction of exact standardized methods in any problem is desirable. In the discussion of thrombocytopenic purpura, perhaps too much attention is devoted to the minor changes in plasma clotting time and to the highly hypothetical "thrombocytolytic activity of the entire reticuloendothelial system." A good discussion of hypothrombinemia, both in adults and in the newborn, is presented.

Whether or not any unusual light has been shed on the problems of coagulation in this monographic presentation of the author's numerous experiments, there can be no question that Nygaard has performed a distinct service by his painstaking and original investigations, which were for the most part performed while he was a fellow in surgery at the Mayo Clinic.

NOTICES

GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held at the Beth Israel Hospital on Tuesday, December 2, at 8:15 p.m.

PROGRAM

The Practice of Medicine in Historical Perspective. Dr. Henry E. Sigerist, professor of the history of medicine and director of the Institute of the History of Medicine, Johns Hopkins University School of Medicine. Discussion will follow by Drs. Hugh Cabot, Reginald Fitz and James C. McCann.

BOSTON DISPENSARY

There will be a clinical staff meeting of the Boston Dispensary in the Pratt Hospital Auditorium on Wednesday, December 10, at 12:30 p.m. Dr. Warfield T. Longcope, physician-in-chief, Johns Hopkins Hospital, Baltimore, will speak on "Virus Pneumonia," and the discussion will be led by Dr. Maxwell Finland. Luncheon will be served at 12 m. All interested members of the profession are cordially invited to attend.

BOSTON HEALTH LEAGUE

A special meeting of the Boston Health League will be held at Perkins Hall, 264 Boylston Street, Boston, on Friday, December 5, at 12:30 p.m. Dr. Harold C. Stuart will speak on "Nutrition in Unoccupied France."

JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

Bennet Street, Boston
Lecture Hall, 9–10 a.m.

MEDICAL CONFERENCE PROGRAM, DECEMBER

Wednesday, December 3 — The Pathologic Physiology of Hypertension: Some recent developments. Dr. R. W. Wilkins.

Friday, December 5 — Errors in Cardiovascular Diagnosis. Dr. Paul D. White.

Monday, December 8 — Clinicopathological conference. Dr. Warfield T. Longcope and Dr. H. E. MacMahon.

Tuesday, December 9 — Medical clinic. Dr. Warfield T. Longcope.

Wednesday, December 10 — Atypical pneumonias. Dr. Lowrey Davenport.

Thursday, December 11 — Epidemiology of Hemolytic Streptococcal Infection. Dr. Chester S. Keefer.

Friday, December 12 — Medical clinic. Dr. Warfield T. Longcope.

Saturday, December 13 — Treatment of Pneumococcal Pneumonia with Sulfadiazine and Serum (motion picture).

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